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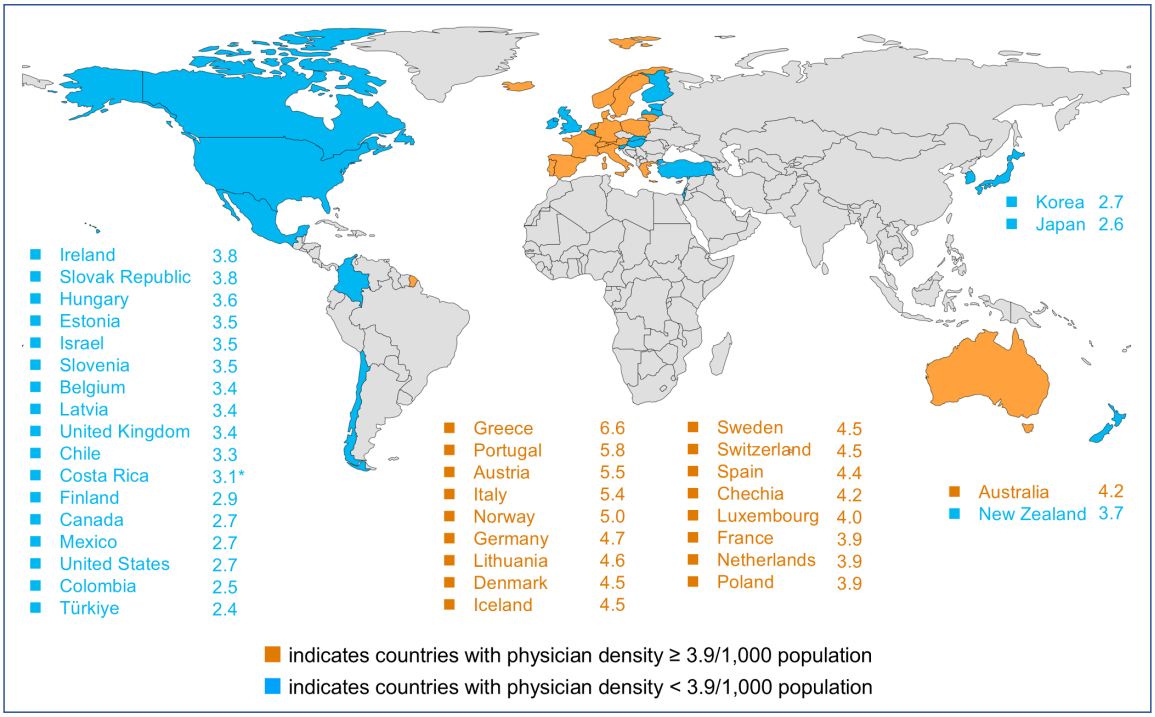

Practising physicians per 1,000 population across OECD countries (Page 2)

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Global Health & Medicine

CONTENTS

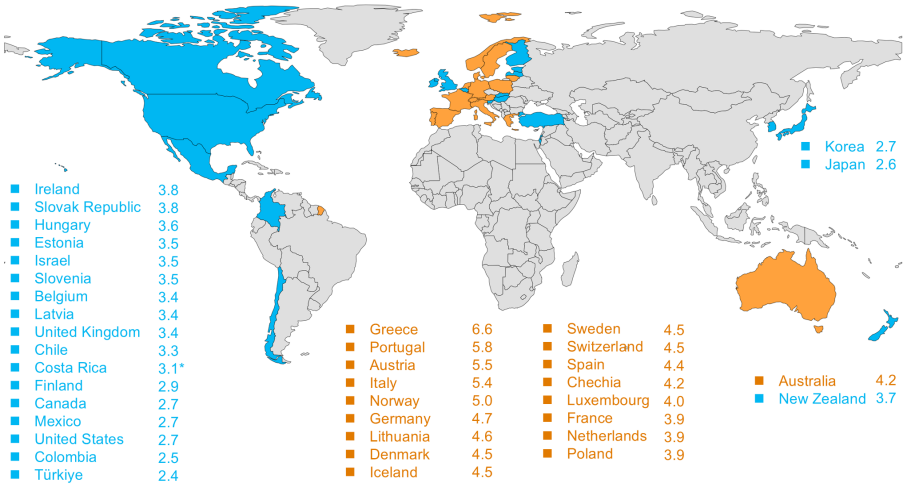
Volume 8, Number 1, 2026

POLICY FORUM

ORIGINAL ARTICLE

CORRESPONDENCE

COVER FIGURE



Practising physicians per 1,000 population across Organisation for Economic Co-operation and Development (OECD) countries. The OECD average is 3.9 physicians per 1,000 population; countries shaded in blue indicate physician density below the average, whereas those shaded in orange indicate density above the average. *Data source*: Health at a glance 2025: OECD Indicators (*https://doi.org/10.1787/8f9e3f98-en*). *No data are available for Costa Rica in Health at a Glance 2025: OECD Indicators. The value for Costa Rica was taken from Health at a Glance 2021: OECD Indicators (*https://doi.org/10.1787/ae3016b9-en*). (Page 2)

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POLICY FORUM

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Regional health security architecture in ASEAN countries: Lessons from regional CDC models and Japan's strategic partnership for ACPHEED development

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Abstract: The COVID-19 pandemic exposed critical gaps in regional health security mechanisms, prompting ASEAN to establish the ASEAN Centre for Public Health Emergencies and Emerging Diseases (ACPHEED), with functions distributed across Indonesia, Thailand, and Vietnam. This policy analysis examines strategic development approaches for ACPHEED through comprehensive benchmarking of the European Centre for Disease Prevention and Control (ECDC), Africa Centres for Disease Control and Prevention (Africa CDC), and Gulf CDC, supported by consultations in Indonesia (2024) and Sweden (2025) involving ASEAN member states and international partners. A comparative analysis reveals distinct organizational models: the ECDC operates within European Union (EU) institutional frameworks emphasizing functional specialization; the Africa CDC employs decentralized Regional Coordination Centers; and the Gulf CDC implements hybrid governance *via* Permanent Communication Networks. Each model offers valuable lessons for ACPHEED's development, particularly concerning governance structures that balance regional coordination with national sovereignty. ACPHEED faces unique challenges due to ASEAN's consensus-based, nonlegislative institutional nature and its tri-country operational structure. Critical success factors include phased surveillance emphasizing a defined scope and capacity building; inclusive governance mechanisms ensuring equitable member-state ownership; and operational frameworks applying subsidiarity principles to complement existing ASEAN mechanisms. Sustainable financing remains paramount given ASEAN's limited budgetary authority. Japan's strategic partnership should capitalize on its technical expertise in laboratory systems, digital surveillance, and disaster preparedness through comprehensive institutional support. ACPHEED's success depends on sustained political commitment, realistic financial arrangements, and effective integration into global health security architectures. This analysis provides a strategic roadmap for ACPHEED's preparatory phase so that it can serve as a regional health security leader while addressing ASEAN-specific institutional constraints.

***Keywords*:** public health emergencies, pandemic prevention, preparedness and response, health security, ASEAN, Japan

1. Introduction

The COVID-19 pandemic highlighted the urgent need for strong regional health security mechanisms to deal with public health emergencies (*1*). In response, ASEAN has moved forward with establishing the ASEAN Centre for Public Health Emergencies and Emerging Diseases (ACPHEED), building on existing regional frameworks such as the ASEAN Coordinating Centre for Humanitarian Assistance on Disaster Management (AHA Centre) and the ASEAN Emergency Operating Centre (EOC) Network for Public Health (*2*). An agreement to establish ACPHEED has not yet been signed, but member states have agreed that ACPHEED's functions will be distributed across Indonesia, Thailand, and Vietnam, with preparations already underway. ACPHEED's development occurs within a global landscape where regional disease control centers have become essential components of international health security architecture (*3*). Notable examples include the European Centre for Disease Prevention and Control (ECDC), the Africa Centres for Disease Control and Prevention (Africa CDC), and the Gulf Center for Disease Prevention and Control (Gulf CDC) (*4*).

This analysis is based on a narrative review of the literature and official documents, as well as comprehensive benchmarking activities conducted in Indonesia (November 2024) and Sweden (September 2025). These consultations involved representatives from the three ACPHEED host countries (Indonesia, Thailand,

and Vietnam), eight ASEAN member states (Brunei, Cambodia, Laos, Malaysia, Myanmar, the Philippines, Singapore, and Timor-Leste), key international partners such as the Japan International Cooperation Agency (JICA), and representatives from the three regional CDCs (*5,6*).

2. Comparative analysis of regional CDC models

The three regional CDCs demonstrate distinct organizational approaches shaped by their unique regional contexts and founding principles (Table 1). Established in 2005, the ECDC operates within the European Union's institutional framework. It is overseen by a Management Board providing strategic direction and an Advisory Forum offering scientific guidance (*5*). The ECDC's structure emphasizes functional specialization, with dedicated units on disease programs, surveillance, preparedness, and corporate services. Its solid legal foundation is supported by the EU's legislative authority (*6*).

The Africa CDC, launched in 2017, adopts a decentralized model through Regional Coordination Centers (RCCs), enabling regional-level coordination while maintaining country representatives for on-the-ground engagement (*7*). This structure reflects the continent's diversity and need for locally adapted approaches, balanced by centralized strategic leadership from the Director General's office and specialized directorates.

The Gulf CDC, established in 2021, implements a hybrid governance model, combining a Supervisory Council responsible for strategic oversight with a Strategic Partnership Council consisting of international experts (*8*). Permanent Communication Networks (PCNs) form expert networks across member states, emphasizing scientific excellence and alignment with regional needs.

2.1. Strategic planning and priority setting

Strategic planning among these centers varies notably in terms of scope and implementation timelines. The ECDC's strategic framework prioritizes enhancing surveillance and preparedness at the EU level, clearly distinguishing short-term objectives such as real-time digital surveillance from mid-term goals (*5*).

The Africa CDC's strategic planning addresses the continent's unique challenges, focusing on strengthening public health systems, enhancing disease surveillance and response, and promoting health security and emergency preparedness (*7*). The center prioritizes building resilience to health emergencies while promoting health research and innovation.

The Gulf CDC's strategic framework demonstrates its adaptation to evolving public health needs, emphasizing comprehensive integration of public health data, collaborative health programs, and improved preparedness for early detection and a rapid response (*8*). Its strong focus on training and capability-building highlights workforce development as a fundamental requirement for effective regional health security.

2.2. Coordination and collaboration mechanisms

Coordination mechanisms across the three centers reflect diverse approaches to managing relationships with member states and engaging international partners. The ECDC uses existing EU institutional frameworks to coordinate with member states while maintaining operational independence at the national level and close collaboration with the World Health Organization (WHO) on joint surveillance activities (*5*).

The Africa CDC prioritizes inter-agency collaboration through partnerships with regional economic communities, global health partners, and civil society organizations (*7*). Its joint action plans with the WHO and other regional organizations demonstrate a commitment to coordinated responses to public health challenges.

The Gulf CDC emphasizes regular engagement through Country Liaison Officers and the establishment of working groups on priority issues (*8*). Its PCNs enable continuous coordination supporting both scientific exchanges and operational collaboration.

2.3. Operational programs and capabilities

Program implementation across these centers reflects adaptation to regional disease burdens and member-state priorities. The ECDC's programs focus on disease surveillance, epidemic intelligence, and preparedness assessments, with notable success in integrating national surveillance systems into a regional framework (*5*). Its training programs in sequencing and bioinformatics highlight the importance of the technical capacity for effective surveillance. Following the COVID-19 pandemic, the ECDC was given an expanded mandate to issue nonbinding scientific recommendations to member states.

The Africa CDC's programmatic portfolio includes integrated disease surveillance and response, strengthening of laboratory networks, coordination of Emergency Operations Centers, and health promotion activities (*7*). The Regional Integrated Surveillance and Laboratory Network (RISLNET) represents an innovative model for resource sharing and specimen exchanges among reference laboratories. Additionally, the Africa CDC is pursuing new financing mechanisms, including the Africa Epidemics Fund as a pooled resource for emergency preparedness and rapid response and the African Pooled Procurement Mechanism to reduce costs and improve access to essential health commodities across the continent (*9*).

The Gulf CDC's programs emphasize preparedness for public health emergencies through landscape analysis,

Table 1. Comparative analysis of regional CDCs: the ECDC, Africa CDC, and Gulf CDC

Aspects	ECDC	Africa CDC	Gulf CDC
Year of establishment	2005	2017 (preparatory phase from 2013)	2021
Legal basis	Solid legal foundation within EU legislative functions	African Union framework	Not specified
Headquarters location	Stockholm, Sweden	Ethiopia (headquarters) + Regional Coordination Centers (RCCs) in Egypt, Nigeria, Gabon, Zambia, and Kenya	Not specified (Gulf Health Council based in Riyadh)
Organizational structure	Functional specialization with dedicated units for disease programs, surveillance, preparedness, and corporate services	Decentralized model with RCCs and country representatives. Central Director General's office with specialized directorates	Hybrid model with Permanent Communication Networks (PCN) creating expert networks across member states
Governance model	Management Board for strategic oversight and Advisory Forum for scientific guidance	Decentralized governance with strong country and regional representation	Hybrid: Supervisory Council for strategic oversight and Strategic Partnership Council with international experts
Budget & funding	Stable funding from the EU budget	Developing innovative financing: Africa Epidemics Fund, African Pooled Procurement Mechanism	Not specified
Core functions	Disease surveillance, epidemic intelligence, preparedness assessments, nonbinding scientific recommendations, and training in informatics and sequencing	Enhancement of healthcare systems, disease surveillance and response, strengthening of laboratory networks, coordination of Emergency Operations Centers, and health promotion	Public health data integration, collaborative programs, early detection and rapid response preparedness, training and capability building, injury prevention, and noncommunicable disease monitoring
Surveillance systems	Integration of preexisting national surveillance systems into the regional framework; real-time digital surveillance	Integrated disease surveillance and response Regional Integrated Surveillance and Laboratory Network (RISLNET)	Comprehensive public health data integration, analytics, and regional surveillance
Laboratory networks	Advanced training and support for laboratory capabilities	RISLNET fosters resource sharing and specimen exchanges among reference laboratories	Not detailed (likely coordinated *via* PCNs)
Outbreak response mechanisms	Preparedness assessments, epidemic intelligence, nonbinding scientific recommendations	Coordination of Emergency Operations Centers and rapid response initiatives	Drills, rapid response frameworks, Country Liaison Officers, and working groups
Research capabilities	Focus on high-level training and integration with research and development	Advance health research and innovation	Analytics, burden-of-disease studies, and achievement of scientific excellence *via* expert networks
Key partnerships	The WHO and national coordinators in member states	Regional Economic Communities, global health partners, civil society, and formal joint actions with the WHO	International experts *via* the Strategic Partnership Council and PCNs
Strengths	Strong legal/institutional basis, functional specialization, stable funding, and EU-wide coordination	Adapted to African diversity, strong interregional cooperation, and innovative funding	Flexible, expert-driven, agile responses, and strong focus on scientific excellence
Challenges	Possible limitations due to reliance on member states' independent operations	Vast geographical area, sustainability of financing, and equitable resource access	Young institution with possible teething challenges
Distinguishing features	EU legislative power and strategic integration capacity; post-COVID mandate for nonbinding advice	Decentralized model with strong regional/local engagement. Innovative funding	PCN-based coordination; hybrid high-level and distributed expert governance; adaptation to fast-changing public health landscapes

Abbreviations: ECDC, European Centre for Disease Prevention and Control; Africa CDC, Africa Centres for Disease Control and Prevention; EU, European Union; WHO, World Health Organization.

simulation exercises, surveillance, and advanced analytics, including burden-of-disease studies, as well as training and capability-building initiatives (*8*). Its focus on regional harm prevention strategies and frameworks for monitoring noncommunicable diseases reflect adaptation to the region's epidemiological transition.

3. Strategic insights into considerations for ACPHEED's preparatory phase

Three key prerequisites shape the strategic development of ACPHEED: *i*) once established, its functions will be distributed across three countries; *ii*) ASEAN has multiple existing health security mechanisms; and *iii*) ASEAN operates by consensus and lacks legislative authority and independent budgetary mechanisms. This comparative analysis has identified several critical factors for the success of ACPHEED's preparatory phase.

First, clear scope definition is fundamental. Successful regional centers typically begin with focused mandates that expand gradually. Accordingly, ACPHEED should initially prioritize infectious disease surveillance, early warning systems, and capacity building, while maintaining flexibility for future functional expansion.

Second, governance and stakeholder engagement are essential foundations. The Gulf CDC experience highlights the importance of inclusive leadership and equitable representation of all member states, while Africa CDC's development underscores the need for strong political commitment (*7,8*). Moreover, because governance and management arrangements during public health emergencies differ from those in routine operations, the experiences of ECDC and Africa CDC during the COVID-19 pandemic provide particularly relevant lessons for ACPHEED.

Finally, operational framework development must strike a balance between regional integration and respect for national systems. The ECDC's principle of subsidiarity—complementing rather than replacing national systems—provides useful guidance for ACPHEED in strengthening and coordinating existing ASEAN public health architectures (*5*).

3.1. Organizational structure

ACPHEED's organizational structure should draw on lessons from all three regional CDCs while remaining tailored to ASEAN's unique institutional context. A hybrid governance model combining strategic oversight by ASEAN health ministers with technical guidance from international experts would provide strong political legitimacy while ensuring scientific rigor.

Functional divisions should align with ACPHEED's established pillar structure, including Prevention; Detection and Risk Assessment; Preparedness and Response; and cross-cutting functions (Figure 1). Additionally, the establishment of country representatives or national focal points, informed by the Africa CDC model, would strengthen member-state engagement and facilitate rapid coordination during public health emergencies (*7*).

Regional nodes or coordination mechanisms should build on existing ASEAN platforms, including the AHA Centre and EOC networks, to avoid duplication and enhance coordination (*10*). This approach would capitalize on ASEAN's established disaster management and disease surveillance capabilities while extending coordination to broader health security challenges.

3.2. Strategic planning framework

Substantial preparatory work has been undertaken to develop ACPHEED's strategic planning framework, including feasibility studies, detailed design studies,

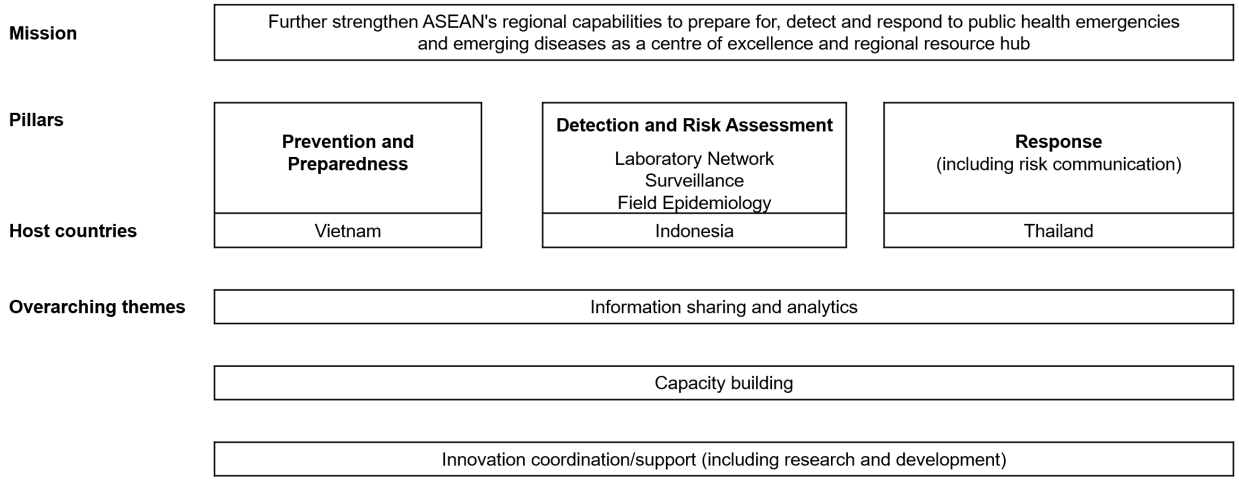

Figure 1. Strategic framework and distributed governance of ACPHEED. ACPHEED operates through a distributed model with three functional pillars hosted by respective Member States: Prevention and Preparedness (Vietnam), Detection and Risk Assessment (Indonesia), and Response (Thailand).

and benchmarking meetings held in Indonesia in 2024. However, the only official document formally endorsed by ASEAN to date is the Scope of Work for the ASEAN Centre for Public Health Emergencies and Emerging Diseases, approved at the ASEAN Health Ministers' Meeting in October 2020. This document defines ACPHEED's mission as "further strengthening ASEAN's regional capabilities to prepare for, detect, and respond to public health emergencies and emerging diseases as a center of excellence and regional resource hub" and outlines strategic focus pillars as well as minimum (1–2 years) and intermediate (3–5 years) capacities.

When the Scope of Work was adopted, ACPHEED was not anticipated to be established across three countries with functions distributed by pillar. This has created gaps between the original framework and current institutional arrangements, making revision of the Scope of Work necessary to align with present realities. Additionally, references to ACPHEED's expected role are already embedded in several ASEAN strategic documents, including the 2020 ASEAN Strategic Framework on Public Health Emergencies, the ASEAN Public Health Emergency Coordination System Framework, and the ASEAN Health Cluster 2 on Responding to All Hazards and Emerging Threats, Work Programme 2021-2025. These policy commitments should be carefully considered in updating ACPHEED's strategic framework (*11-13*).

ASEAN member states, particularly the three host countries, must therefore conduct parallel discussions on the strategic planning framework. In doing so, the three host countries should ensure not only internal coherence within each host pillar, but also overall functional integration and strategic coherence of ACPHEED.

Finally, although long-term goals are not specified in the Scope of Work, ACPHEED should aim to evolve into a regional health security hub integrated with the WHO and broader global healthcare systems, maintaining distinctive capabilities tailored to ASEAN's disease burden patterns and regional challenges (*14-16*).

3.3. Coordination and collaboration mechanisms

ACPHEED's coordination mechanisms should include PCNs modeled on the Gulf CDC approach, establishing expert networks across ASEAN member states organized by technical specialties (*8*). These networks would enable continuous knowledge exchange and support rapid mobilization of technical expertise during public health emergencies.

Resource and data sharing platforms should support the pooling of laboratory capacities, genomic sequencing facilities, and emergency stockpiles. Shared data analysis platforms for real-time surveillance and outbreak modeling would enhance regional preparedness while respecting sovereignty over health-related data.

Unlike the European Union, ASEAN lacks legislative authority, so formal collaboration instruments will be essential to enable timely information and resource exchanges and to provide legal and operational frameworks for cross-border coordination during public health emergencies.

3.4. Finance

Because ASEAN lacks an independent budget, funding for ASEAN centers is set by their Establishment Agreements and typically combines host-country support, equal and voluntary member-state contributions, and external partner funding. Conversely, the ECDC is financed through the EU budget, ensuring greater financial stability and institutional independence. Although the AHA Center includes equal member states' contributions, it still relies heavily on external partners for operational funding (*17*).

To ensure ACPHEED's long-term sustainability and institutional independence, securing a predictable and permanent funding source is essential. This will require clearly demonstrating added value to member states and partners by strengthening, rather than duplicating, existing ASEAN mechanisms.

The tri-country operational model also complicates financial management, particularly fund flows across the three centers. Efficient operation will require transparent, equitable, and practical financial arrangements.

4. Japan's strategic role in ACPHEED's development: Historical context and comparative advantages

Japan's involvement in health security in ASEAN countries has evolved from primarily bilateral technical cooperation to broader multilateral support (*18*). Japan's experience in developing strong public health systems, advanced surveillance infrastructure, and disaster preparedness mechanisms provides important technical foundations for ACPHEED. Within this policy context, the Japan Institute for Health Security (JIHS) functions as a core technical implementing institution, mobilizing expert capacity to support regional health security initiatives, including advisory and capacity-building inputs relevant to ACPHEED's preparatory and institutional development processes (*19*).

Japan's comparative advantages in supporting ACPHEED include advanced laboratory technologies, health informatics, and digital surveillance systems, workforce development, and experience in building and sustaining regional cooperation frameworks (*20*). Japan's responses to emerging infectious disease threats demonstrate practical expertise in epidemic intelligence, risk assessment, and coordinated responses (*21*).

4.1. Strategic engagement framework

Japan's strategic engagement with ACPHEED should

extend to include sustained technical cooperation, capacity-building support, financial contributions, and institutional development assistance (*18*). Technical cooperation should prioritize areas in which Japan has strong comparative advantages, such as enhancement of laboratory networks, surveillance system integration, and development of digital health platforms.

Capacity-building support should emphasize workforce development through fellowship programs, technical exchanges, and joint training initiatives. Japan's experience in field epidemiology training and public health emergency management provides valuable models for ACPHEED's development strategies.

Financial contributions should combine direct funding with in-kind technical assistance, leveraging Japan's Official Development Assistance frameworks and mechanisms for regional cooperation (*18,20*). This approach should emphasize long-term sustainability by facilitating a gradual transition from donor-driven support to increased ownership and financial commitment by ASEAN member states for ACPHEED's operations.

4.2. Institutional development support

Japan's institutional development support should focus on strengthening governance structures, developing operational frameworks, and facilitating strategic partnerships (*18-21*). Governance support can draw on Japan's experience with mechanisms of regional cooperation to help ACPHEED establish effective decision-making processes.

ACPHEED's operational framework should draw on Japan's expertise in disaster management coordination, responses to public health emergencies, and cross-sectoral collaboration. Additionally, Japan's experience with One Health approaches and environmental health monitoring can provide valuable guidance for ACPHEED (*4,22*).

In terms of partnership facilitation, Japan can serve as a bridge between ACPHEED and global health security networks. By leveraging its strong relationships with the WHO, G7 health security initiatives, and other regional CDC networks, Japan can support ACPHEED's deeper integration into international surveillance, preparedness, and response systems.

4.3. Long-term strategic partnership

Japan's long-term engagement with ACPHEED should evolve beyond support for its establishment toward a strategic partnership focused on collaboration in innovation, research and development, and integration within global health security frameworks (*18,23*). Innovation efforts should emphasize the joint development of surveillance technologies, diagnostic tools, and response mechanisms tailored to ASEAN's unique health security challenges.

Research and development support should foster collaborative programs addressing regional disease burdens, antimicrobial resistance, and climate-sensitive health risks. Japan's strong research institutions and pharmaceutical industry offer valuable resources to advance ACPHEED's scientific and technological capabilities (*23*).

Global health security integration should position the Japan–ACPHEED partnership as a model for regional cooperation, contributing to the broader global health security architecture while focusing on ASEAN's specific needs and priorities (*14,16,24*).

5. Conclusion

The establishment of ACPHEED presents both major opportunities and significant challenges for ASEAN's regional health security. Effective regional disease control requires balancing regional coordination with national sovereignty, ensuring clear governance with strong member-state ownership, and maintaining operational flexibility to respond to evolving health threats.

ACPHEED should prioritize a clearly defined mandate, inclusive governance mechanisms, and phased implementation in line with existing ASEAN health frameworks. Its success will depend on sustained political commitment, effective coordination, and strong partnerships with international networks.

Japan's strategic engagement with ACPHEED offers benefits. By providing this support, Japan can serve as ACPHEED's primary strategic partner by providing valuable technical expertise, financial resources, and experience in regional cooperation for ACPHEED's establishment, long-term sustainability, and ASEAN's objectives for broader regional integration.

Ultimately, ACPHEED's success should be measured not only by its emergency response capacity but also by its contribution to strengthening national healthcare systems, enhancing regional coordination, and positioning ASEAN as a leader in global health security cooperation. A strong Japan–ACPHEED partnership can advance these goals and demonstrate the value of international collaboration in addressing shared health challenges.

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Japan's high-quality healthcare system despite physician shortages: Exploring the paradox and pathways toward sustainable healthcare

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Abstract: Japan's rapidly aging population presents significant demographic pressures, and yet the country maintains high standards of healthcare delivery with remarkably low rates of preventable and treatable mortality. According to the latest data from the Organisation for Economic Co-operation and Development (OECD), Japan ranks 35th among 38 countries in physician density (2.6 per 1,000 population), and yet it records 12.1 physician consultations per person per year—among the highest in the OECD. This article analyzes this paradoxical situation—where high medical performance is maintained despite relatively few physicians—by examining both institutional strengths and emerging vulnerabilities. The strengths include universal health insurance with high public funding; a resource-intensive medical infrastructure; and a robust support network of allied healthcare professionals. Simultaneously, we identify the following vulnerabilities: increasing demand intensity; shortages and an uneven distribution of physicians; hospital financial losses; the limitations of effective gatekeeping under free access systems; and the amplified workload resulting from the concentration of authority and responsibility among physicians. Moreover, we examine initiatives needed to ensure the sustainability of insurance-based healthcare, including: redesigning supply-demand planning and education policies; expanding task sharing and securing funding sources; designing incentives for essential and regional healthcare services; and restructuring access models to value-based utilization and need-based care.

***Keywords*:** physician shortage, super-aged society, healthcare workforce, healthcare resource allocation, health policy, Japan

1. Introduction

Japan faces the world's fastest aging of the population. By September 2025, individuals aged 65 years and older constituted 29.4% of the total population (*1*), representing the highest proportion among the Organisation for Economic Co-operation and Development (OECD) member nations. Even though aging places significant strain on healthcare systems through increased chronic disease prevalence and healthcare demand, Japan has consistently maintained exceptionally high healthcare outcomes—not only in terms of life expectancy but also through low rates of preventable and treatable mortality (*2*).

Public satisfaction with healthcare access and quality is also remarkably high. Approximately 80% of Japanese residents report satisfaction with the medical care they receive, significantly exceeding the OECD average of about 64% (*2*). According to the 2025 edition of Health at a Glance, Japan's annual physician visits per individual stood at 12.1, ranking second in the OECD after South Korea's 17.5 visits (*3*). However, the same paper reports that Japan has 2.6 practicing physicians per 1,000 population, ranking 35th among 38 OECD member countries (with data for Costa Rica unavailable, Japan ranks third lowest among countries with available data); this ratio is significantly below the OECD average of 3.9 physicians per 1,000 population (Figure 1).

2. Structural strengths of Japan's healthcare system

2.1. A universal health insurance system and public financing

Japan operates a universal health insurance system with nearly 100% coverage, ensuring equal access to necessary medical care regardless of income or employment status (*2,3*). Out-of-pocket expenses are

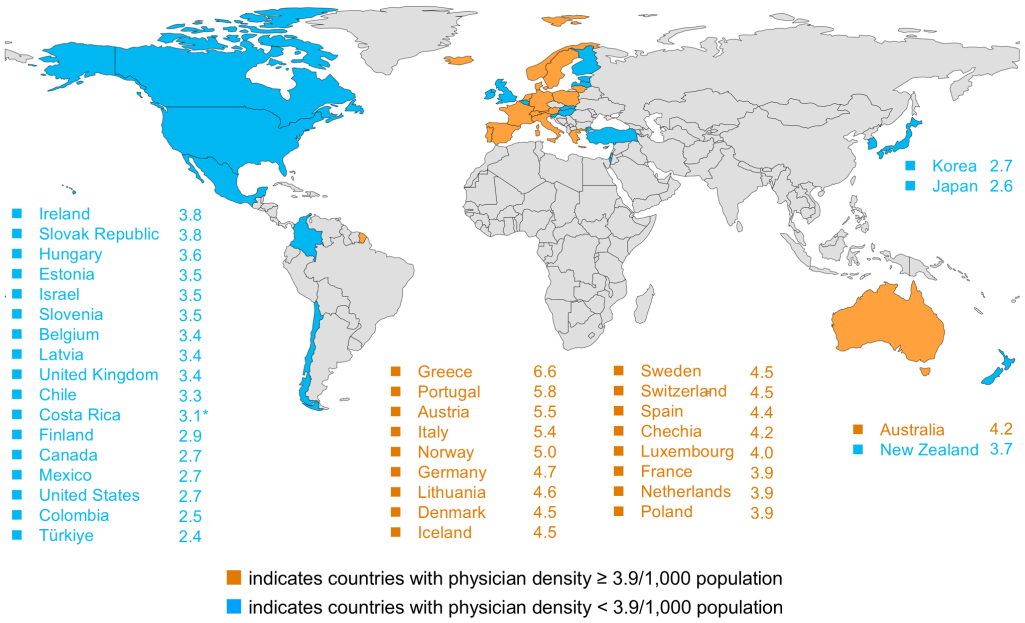

Figure 1. Practising physicians per 1,000 population across Organisation for Economic Co-operation and Development (OECD) countries. The OECD average is 3.9 physicians per 1,000 population; countries shaded in blue indicate physician density below the average, whereas those shaded in orange indicate density above the average. *Data source*: Health at a glance 2025: OECD Indicators (*https://doi.org/10.1787/8f9e3f98-en*). *No data are available for Costa Rica in Health at a Glance 2025: OECD Indicators. The value for Costa Rica was taken from Health at a Glance 2021: OECD Indicators (*https://doi.org/10.1787/ae3016b9-en*).

generally limited to no more than 30% for individuals age 6–69, while those age 70 and older pay 10–30% depending on income, and children under 6 pay 20%. In addition, cost sharing mechanisms such as the High cost Medical Expense Benefit system are designed to prevent households from facing sudden financial burdens due to medical costs. (*4*). Public funding and mandatory insurance contributions account for approximately 85% of total healthcare expenditures, surpassing the OECD average of 75% (*2*).

2.2. A robust healthcare infrastructure

Japan possesses one of the most resource-intensive healthcare infrastructures globally. The country maintains approximately 13 hospital beds per 1,000 population – three times the OECD average of 4 beds (*2*). Japan also leads OECD countries in the per-capita availability of advanced diagnostic equipment, including CT and MRI scanners (*2*).

2.3. A strong nursing and allied healthcare workforce

Japan's nursing workforce density of 12.2 nurses per 1,000 population significantly exceeds the OECD average of 9.2 nurses (*3*). The physician-to-nurse ratio (1:4.6) is among the highest among OECD countries, enabling partial task shifting and contributing to improved patient satisfaction (*3*). Pharmacists also play an expanded role in community-based care, actively participating in prescription drug review and medication management (*5*).

3. The nature of Japan's physician shortage

3.1. Growing demand among a super-aged society

Japan's physician shortage cannot be simply assessed by raw numbers alone. Older patients typically present with multimorbidity, polypharmacy, and frequent healthcare needs, leading to exceptionally high healthcare utilization rates (*6*). As mentioned earlier, Japan ranks among the OECD nations with the highest outpatient physician consultation rates per capita (*3*), significantly increasing physicians' workload even when the absolute number of physicians remains stable.

3.2. Supply constraints due to policy limitations

Historically, Japan has maintained strict control over medical school enrollment as part of efforts to manage healthcare costs while maintaining quality standards (*7*). However, in response to the emerging physician shortage, the government implemented two measures: the "Comprehensive measures to increase the supply of physicians" in 2006, which added 10 additional students each in 10 prefectures with severe physician shortages, and the "Urgent measures to increase the supply of physicians" in 2007, which increased enrollment quotas by 5 students each in every prefecture. These initiatives raised total medical school enrollment to 7,793 in 2008.

Subsequent efforts to increase the regional number of physicians and train research physicians have led to rising enrollment quotas (*7*), resulting in an actual increase in the number of physicians (Figure 2).

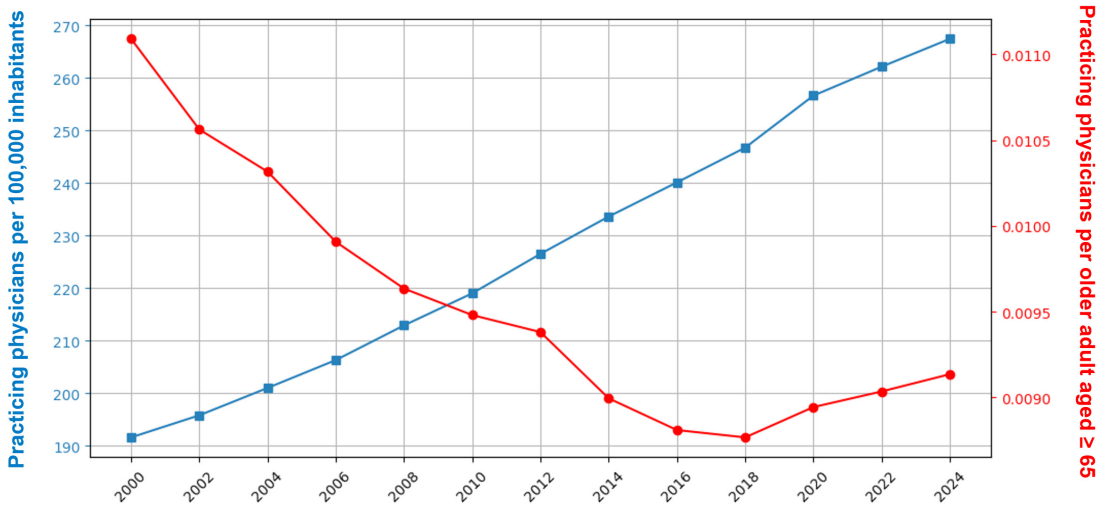

Figure 2. Trends in the number of practicing physicians overall (blue line) and the number of physicians per older adult aged 65 years and older (red line) in Japan, 2000–2024. The blue line represents the number of practicing physicians per 100,000 inhabitants, and the red line represents the number of practicing physicians per older adult aged 65 years and older. *Data source: Ref. (1,10).*

However, the combined effect of expanded medical school enrollments in 2008 and stable growth of the population aged 65 years and older since 2020 has only recently begun to increase physicians per elderly individual, with supply still struggling to keep pace with demand due to the time required for physician training (Figure 2). As of 2024, Japan has approximately 36.24 million people aged 65 years and older and 331,092 physicians. This translates to an average of about 110 older adults per physician when calculated as a population-to-physician ratio (*1,10*).

3.3. Regional and specialty-specific maldistribution

A critical factor contributing to Japan's physician shortage is not merely the absolute number of physicians, but rather the significant regional and specialty-based maldistribution. The Ministry of Health, Labour and Welfare's incentive policies–which provide financial and professional benefits to physicians who practice in areas with few physicians–have led to an increase in young physicians working in these underserved prefectures in recent years, resulting in gradual reductions in the number of prefectures with a shortage of physicians (*8*). Nevertheless, rural and peripheral regions continue to face challenges in recruiting and retaining physicians, leaving residents with limited access to emergency care and comprehensive primary medical care (Figure 3).

In contrast, urban areas have experienced a concentration of physicians, particularly in elective and private practice specialties like cosmetic surgery, where physicians are increasingly drawn by higher income potential and better work-life balance opportunities (*9*). Statistics on physicians, dentists, and pharmacists published by the Ministry of Health, Labour and Welfare every two years indicate that between 2000 and 2024, the number of surgeons declined from 24,444 to 12,341—nearly half—while the number of physicians specializing in cosmetic surgery increased more than eightfold, rising from 212 to 1,720 (*10*).

4. Financial burdens and organizational vulnerabilities in hospital administration

Approximately 70% of Japanese hospitals operate at a financial deficit (*11*), primarily due to: *i*) reduced reimbursement rates under the national medical fee structure; *ii*) rising personnel and energy costs; and *iii*) declining inpatient volumes in rural areas (*12*). These financial pressures can significantly impair hospitals' ability to attract physicians, particularly in high-demand specialties such as emergency medicine, internal medicine, obstetrics and gynecology, and surgery. Ministry of Health, Labour and Welfare surveys indicate varying levels of financial distress by type of hospital: 40.0% of convalescent hospitals; 56.3% of chronic-care hospitals; 75.0% of super-acute care hospitals; 77.8% of Type A acute-care hospitals; and 73.0% of Type B acute-care hospitals reported a deficit in fiscal 2024, with higher deficits observed in hospitals providing more advanced medical care (*12*). This situation creates a vicious cycle where the staffing shortages further compromise hospital sustainability.

5. Limitations of effective gatekeeping mechanisms

While Japan formally operates a tiered healthcare delivery system, patients can access secondary/tertiary hospitals without a referral, typically with additional out-of-pocket charges (*13*). In practice, large hospitals frequently accommodate patients with low-acuity conditions, creating excessive workloads for physicians

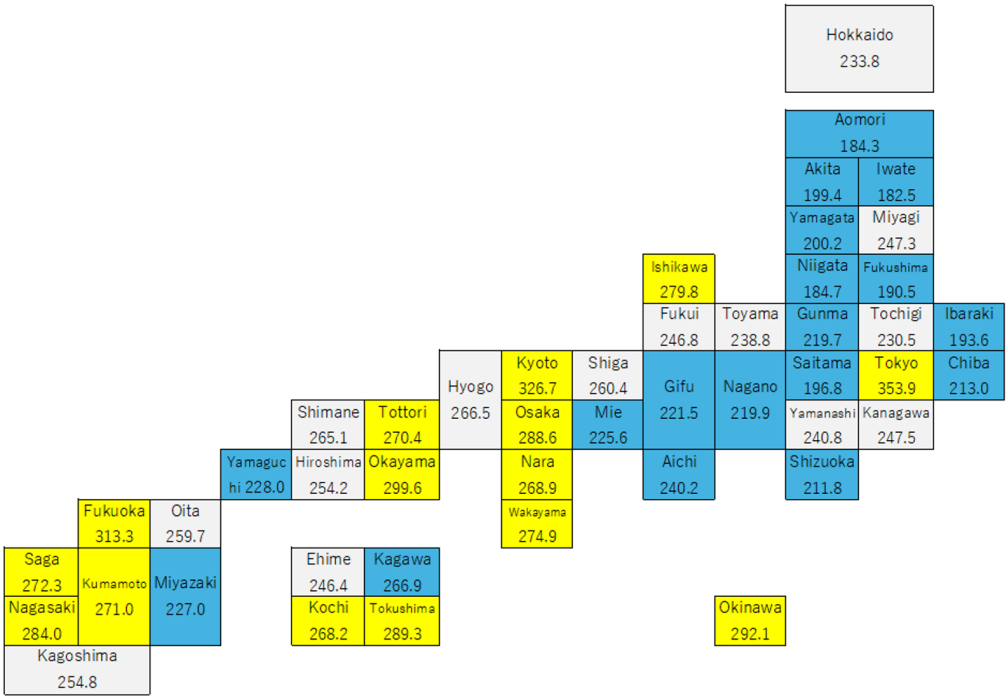

Figure 3. Physician maldistribution across prefectures in Japan. Blue indicates prefectures in the lower third of the distribution (severe maldistribution with a stronger tendency toward physician shortage; index values ≤ 228.0), gray represents the middle range (average distribution; index values 230–266), and yellow denotes prefectures in the upper third (less maldistribution or a tendency toward physician surplus; index values ≥ 266.9). The physician maldistribution index is defined as the ratio of the standardized number of physicians to regional healthcare demand, with regional healthcare demand calculated as the population per 100,000 multiplied by the standardized healthcare utilization rate. *Data source: Ref. (8)*.

and reducing the overall efficiency of the healthcare system (*13*). A 2016 study by Moriwaki *et al*. found that, when analyzing visits per patient, approximately 40% of patients at large hospitals with 200+ beds were presented with low-acuity conditions (*14*). Legal and societal expectations discourage healthcare providers from refusing treatment, further limiting effective gatekeeping.

6. Physicians as a systemic bottleneck

Despite Japan's extensive medical infrastructure and support staff, physicians remain the primary decision-makers and parties legally responsible for providing healthcare. Regulatory frameworks and professional boundaries constrain task shifting, concentrating diagnostic and treatment authority among physicians and exacerbating workload pressures (*15*). As a result, physician shortages have emerged as a critical bottleneck resource within the system.

To address physician workload issues, the Ministry of Health, Labour and Welfare established the Committee to Promote Task Shifting/Sharing to identify and publish feasible task transfers to related professions, and particularly nurses and pharmacists (*16*). Before the committee's establishment, the Japan Medical Association Federation raised concerns that the funding source for task shifting–relying on revised medical fees–could actually make staff recruiting more challenging for hospitals under financial constraints (*17*). The association emphasized the necessity of nationwide fiscal measures, including adjusting medical fees, as essential solutions (*17*).

7. Policy implications

The Japanese case suggests that addressing physician shortages requires structural measures including:

i) Addressing physician shortages and regional imbalances. The supply of physicians should be improved and demand planning and educational policies should be implemented (*7,8*).

ii) Decentralizing physician authority and workload. Task sharing with nurses, pharmacists, and other allied healthcare professionals should be expanded while securing necessary funding (*15-17*).

iii) Implementing financial incentives for rural healthcare and essential medical care (*8*). Additional allowances for physicians working in regions with a shortage of physicians should be enhanced and career development for physicians graduating from medical schools with regional quotas should be supported.

In conclusion, Japan's physician shortage is not caused by failures in universal health coverage, but rather stems from structural imbalances involving extreme demand intensity, a limited healthcare workforce, and

mechanisms of institutional allocation., Ensuring that there is one physician per person aged 65 years and older will become increasing difficult, as the graph shows, so both types of measures are needed: maintaining healthcare quality with minimal regional disparities, and implementing strategies to keep physicians working in each region and specialty. Without more effective institutional reforms, this imbalance risks undermining the long-term sustainability of one of the world's most highly regarded healthcare systems.

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Regional and facility-type variations in infectious diseases in childcare and early childhood education facilities in Japan during the COVID-19 pandemic: A nationwide cross-sectional questionnaire survey

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Abstract: Young children are susceptible to infectious diseases due to their developing immune systems and close contact in group care settings. During the coronavirus disease 2019 (COVID-19) pandemic, infection prevention measures may have altered the epidemiology of common childhood infections, yet evidence on variations by facility type and region remains limited. In this study, the occurrence of COVID-19 and child-specific infectious diseases in childcare and early childhood education facilities in Japan was examined with particular focus on facility type and regional population density. A nationwide mail survey was conducted between January and April 2023 among 5,000 facility managers, and 710 valid responses were analysed. Over 90% of facilities reported at least one COVID-19 case within the previous year. The occurrence of child-specific infectious diseases, including adenovirus infection, hand, foot, and mouth disease, herpangina, streptococcal infection, norovirus infection, and respiratory syncytial virus infection, was lower in kindergartens serving children aged ≥ 3 years than in children in daycare centres or certified childcare centres ($p < 0.05$). Hand, foot, and mouth disease and influenza virus infection showed significant linear associations with population density, with lower reporting rates in less densely populated regions ($p < 0.05$). Conversely, rotavirus infection was more frequently reported in low-density regions ($p < 0.05$), whereas other child-specific infectious diseases exhibited heterogeneous and non-linear regional patterns, indicating that population density alone does not explain regional variation. These results highlight the importance of facility-, age-, and region-specific approaches to infection prevention in childcare settings beyond the COVID-19 pandemic.

***Keywords*:** infection surveillance, population density, infection prevention, early childhood health, childcare systems, public health measures

1. Introduction

Infectious diseases spread easily in childcare and early childhood education facilities, where young children spend extended periods in close contact during daily activities and rest. During the coronavirus disease 2019 (COVID-19) pandemic, children in Japan experienced substantial infection waves; notably, infections among children increased markedly during the sixth wave (January to March 2022) (*1*). Morimoto *et al.* reported that 30.5% of confirmed COVID-19 cases in Kyoto Prefecture during this period occurred in children aged ≤ 9 years (*2*). At the same time, widespread infection prevention measures implemented in childcare settings, such as mask-wearing, hand hygiene, and the use of alcohol-based sanitisers, were associated with a marked decline in other child-specific infectious diseases, including influenza, respiratory syncytial virus (RSV), norovirus, and adenovirus gastroenteritis (*3*).

Despite heightened interest in infection control during the pandemic, evidence regarding the occurrence of non–COVID-19 infectious diseases in childcare settings remains limited. Previous studies on infectious disease outbreaks in daycare centres in Japan were conducted before the pandemic (*4*), and no nationwide research has comprehensively examined child-specific infectious diseases across different types of childcare and early childhood education facilities during the COVID-19 pandemic.

The Japanese childcare and early childhood education system comprises three main facility types: kindergartens, daycare centres, and certified childcare

centres (*5*). Kindergartens, administered by the Ministry of Education, Culture, Sports, Science and Technology, admit children aged ≥ 3 years, regardless of parental employment status (*6,7*). Daycare centres, overseen by the Child and Family Agency, primarily serve children from infancy whose parents require childcare owing to employment or specific circumstances (*6,7*). Certified childcare centres integrate the functions of daycare centres and kindergartens, serving children from infancy to 5 years of age (*6,7*). Differences in age composition, operational structure, and daily routines across these facility types may differentially influence the occurrence and transmission of infectious diseases.

International studies suggest that infectious disease patterns among children vary by age group and regional characteristics. For example, Shen *et al.* reported age-related differences in the incidence of hand, foot, and mouth disease during the COVID-19 outbreak in China (*8*). In addition, Shirabe *et al.* demonstrated a strong association between population density and COVID-19 infection rates in Japan, indicating that regional context may also affect the occurrence of child-specific infectious diseases (*9*).

Understanding the occurrence of infectious diseases by facility type and region is essential for implementing timely and appropriate infection prevention measures. Prior research has shown that early recognition of infection trends within daycare centres facilitates prompt interventions and effective disease control (*10*). However, nationwide data examining child-specific infectious diseases, including COVID-19, across different childcare and early childhood education settings in Japan during the pandemic are lacking.

Therefore, the aim of this study was to clarify occurrence of COVID-19 and other child-specific infectious diseases in kindergartens, daycare centres, and certified childcare centres across Japan during the COVID-19 pandemic, with a particular focus on differences by facility type and regional population density.

2. Survey respondents and Methods

2.1. Study design

This study was a nationwide, cross-sectional survey conducted using self-administered questionnaires. Facilities were randomly selected from the 39,706 childcare and early childhood education facilities registered in the 2022 National School Data in Japan (*11*). The required sample size was calculated assuming a 95% confidence level, a 3% margin of error, and a population ratio of 0.5, resulting in a target sample of 1,040 facilities. Given the national childcare survey response rate of 23.9% (*12*), at least 4,426 facilities were required to achieve the target sample size; therefore, 5,000 facilities were contacted to account for a potential lower response rate caused by survey complexity.

2.2. Participants

In this study, managers of major Japanese childcare and early childhood education facilities were targeted, including kindergartens, daycare centres, and certified childcare centres. Self-administered questionnaires and return envelopes were mailed to the selected facilities.

2.3. Regional classification

Based on facility locations, the regions of Japan were divided into nine areas: Hokkaido, Tohoku, Kanto, Hokuriku/Koshinetsu, Tokai, Kinki, Chugoku, Shikoku, and Kyushu/Okinawa (Figure 1). The Hokkaido region comprised only the Hokkaido prefecture, while the Tohoku region included Aomori, Akita, Yamagata, Miyagi, Iwate, and Fukushima prefectures. The Kanto region comprised Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, and Kanagawa prefectures. Hokuriku/Koshinetsu region included Toyama, Ishikawa, Fukui, Yamanashi, Nagano, and Niigata prefectures; Tokai region comprised Gifu, Shizuoka, Aichi, and Mie prefectures; and the Kinki region included Shiga, Kyoto, Osaka, Hyogo, Nara, and Wakayama prefectures. The Chugoku region comprised Tottori, Shimane, Okayama, Hiroshima, and Yamaguchi prefectures; Shikoku region included Tokushima, Kagawa, Ehime, and Kochi prefectures; and Kyushu/Okinawa region included Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki,

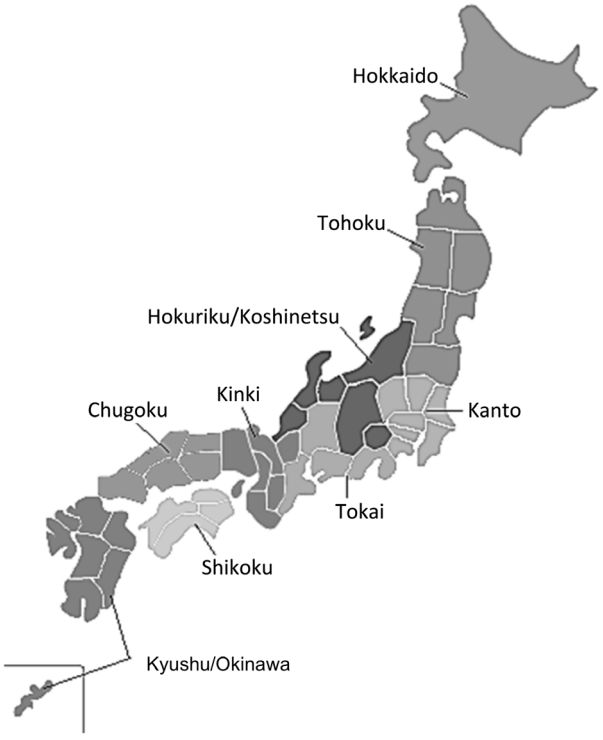

Figure 1. Regional classification of Japan used in this study.

Kagoshima, and Okinawa prefectures.

Furthermore, regions were classified into low, medium, and high density for the population density analysis. Population density (persons per km²) was calculated at the prefectural level using data obtained from the Japan Statistics e-Stat database (*13*). For each region, the median population density of the prefectures included was used as a representative value. Based on these median values, regions were classified into low-, medium-, and high-density categories. Low-density regions included Hokkaido, Tohoku, and Hokuriku/Koshinetsu; medium-density regions comprised Chugoku, Shikoku, and Kyushu/Okinawa; and high-density regions included Kanto, Tokai, and Kinki.

2.4. Questionnaire content

The questionnaire was used to collect information on managers' demographics, facility type and location, the number of childcare workers, and the number of children at each facility. In addition, data on whether each facility had reported cases of COVID-19 and other child-specific infectious diseases, including adenovirus, hand, foot, and mouth disease, herpangina, streptococcal infection, influenza virus, norovirus, rotavirus, RSV, and mumps, within the past year were obtained.

2.5. Statistical analysis

Categorical variables are presented as numbers and percentages (%), whereas continuous variables are expressed as means and standard deviations (SD). The proportion of facilities reporting each child-specific infectious disease was analysed based on facility type and region. Regional population density was defined using prefecture-level population density data obtained from official national statistics. Chi-square tests and residual analysis were performed to determine differences among facility types and regions within the 1-year period. Adjusted residuals greater than 1.96 or less than −1.96 were considered statistically significant. For analyses involving ordered population density categories (low, medium, and high), linear-by-linear association tests were additionally conducted to assess linear trends. All analyses were conducted using SPSS version 26.0, and a p-value < 0.05 was considered statistically significant.

2.6. Ethical considerations

The survey request documents, including questionnaires and return envelopes, were sent to all selected facilities. Informed consent was obtained when the managers read the request, completed the questionnaire, and returned it. This study was approved by the Research Ethics Review Board of Chukyogakuin University (Approval No. 22-04) and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

3. Results

3.1. Basic information

In December 2022, questionnaires were randomly sent to 5,000 facility managers, and 776 responses (response rate: 15.4%) were received between January and April 2023. Of these, 66 responses with incomplete basic information or multiple uncertainties were excluded, resulting in 710 responses (valid response rate: 14.2%). Among the responses, 15.5% were from kindergartens, 53.5% from daycare centres, and 31.0% from certified childcare centres. By region, responses were as follows: 27.4% from Kanto, 13.0% from Kyushu/Okinawa, 12.1% each from Tohoku and Kinki, 10.7% from Tokai, 8.7% from Hokuriku/Koshinetsu, 7.0% from Chugoku, 5.5% from Hokkaido, and 3.5% from Shikoku (Table 1).

The mean age of the managers was 55.2 (SD 9.6) years. By facility type, the average ages were 55.7 (SD 9.3) years for kindergartens, 55.3 (SD 9.4) years for daycare centres, and 54.7 (SD 10.0) years for certified childcare centres. The average number of childcare workers per facility was 30.8 (SD 23.4): 19.3 (SD 15.3) in kindergartens, 31.9 (SD 22.9) in daycare centres,

Table 1. Regional distribution of childcare and early childhood education facilities by facility type (n = 710)

Region	Kindergartens *n* (%)	Daycare centres *n* (%)	Certified childcare centres *n* (%)	Total *n* (%)
Hokkaido	7 (18.0)	19 (48.7)	13 (33.3)	39 (5.5)
Tohoku	13 (15.1)	40 (46.5)	33 (38.4)	86 (12.1)
Kanto	35 (18.0)	124 (64.0)	35 (18.0)	194 (27.4)
Hokuriku/Koshinetsu	3 (4.8)	27 (43.6)	32 (51.6)	62 (8.7)
Tokai	15 (19.7)	36 (47.4)	25 (32.9)	76 (10.7)
Kinki	15 (17.4)	38 (44.2)	33 (38.4)	86 (12.1)
Chugoku	12 (24.0)	29 (58.0)	9 (18.0)	50 (7.0)
Shikoku	7 (28.0)	11 (44.0)	7 (28.0)	25 (3.5)
Kyushu/Okinawa	3 (3.2)	56 (60.9)	33 (35.9)	92 (13.0)
Total	110 (15.5)	380 (53.5)	220 (31.0)	710 (100)

Note: Values are presented as *n* (%). Percentages for facility types are calculated within each region, whereas percentages in the total column represent the proportion of all facilities.

and 34.8 (SD 25.8) in certified childcare centres. The average number of children per facility was 96.8 (SD 57.9). By type, kindergartens had a mean of 95.0 (SD 73.6) children, daycare centres had 83.8 (SD 43.5), and certified childcare centres had 120.3 (SD 63.7) (Table 2).

3.2. One-year facility-level reporting rates of infectious diseases

COVID-19 infections were reported in 96.9% of the facilities over the past year. However, norovirus and influenza virus infections, which are prevalent every year, were reported in 20.4% of the facilities. Adenovirus infection was reported in 52.8%, hand, foot, and mouth disease in 66.5%, herpangina in 36.2%, streptococcal infection in 48.7%, RSV infection in 63.8%, and mumps in 8.5% of the facilities.

3.3. One-year facility-reported infectious diseases by facility type

Statistical analysis revealed significant differences among facility types in the 1-year reporting rates for adenovirus infection, hand, foot, and mouth disease, herpangina, streptococcal, influenza virus, norovirus, rotavirus, and RSV infections (Table 3). Adjusted residuals greater than 1.96 or less than −1.96 indicated significantly higher or lower 1-year facility-level reporting rates than expected. Significant differences in 1-year facility-level reporting rates for adenovirus and hand, foot, and mouth disease were observed among facility types, as indicated by adjusted residuals. Residual analysis for adenovirus infection revealed values of −6.5 for kindergartens, 2.3 for daycare centres, and 2.6 for certified childcare centres. Regarding hand, foot, and mouth disease, adjusted residuals were −7.5 for kindergartens, 3.2 for daycare centres, and 2.4 for certified childcare centres. Significant differences in the 1-year facility-level reporting rates of herpangina and RSV infection were observed between kindergartens and daycare centres. Specifically, adjusted residuals for herpangina were −6.2 for kindergartens and 3.5 for daycare centres. For the RSV infection, the adjusted residuals were −5.2 for kindergartens and 2.7 for daycare centres. Residual analysis showed significant differences in 1-year facility-level reporting rates for streptococcal and norovirus infections between kindergartens and certified childcare centres, whereas for rotavirus infection, a significantly lower reporting rate was observed only in kindergartens. For streptococcal infections, the adjusted residual was −3.9 for kindergartens and 3.7 for certified childcare centres. Similarly, for norovirus infection, the adjusted residuals were −3.7 and 2.6 for kindergartens and certified childcare centres, respectively. For rotavirus infection, the adjusted residuals were −2.5 for kindergartens.

Table 2. Characteristics of facilities and managers by facility type (*n* = 710)

	Kindergartens (*n* = 110)	Daycare centres (*n* = 380)	Certified childcare centres (*n* = 220)	Total (*n* = 710)
Age of managers (years)	55.7 (9.3)	55.3 (9.4)	54.7 (10.0)	55.2 (9.6)
Number of childcare workers	19.3 (15.3)	31.9 (22.9)	34.8 (25.8)	30.8 (23.4)
Number of children	95.0 (73.6)	83.8 (43.5)	120.3 (63.7)	96.8 (57.9)

Note: Values are presented as mean (standard deviation).

Table 3. One-year facility-level reporting rates of child-specific infections (*n* = 710)

	Facilities reporting infection, *n* (%)			
	Kindergartens (*n* = 110)	Daycare centres (*n* = 380)	Certified childcare centres (*n* = 220)	Total (*n* = 710)
COVID-19 infection	106 (96.4)	367 (96.6)	215 (97.7)	688 (96.9)
Adenovirus infection*	27 (24.5)[#]	216 (56.8)[##]	132 (60.0)[##]	375 (52.8)
Hand, foot, and mouth disease*	39 (35.5)[#]	273 (71.8)[##]	160 (72.7)[##]	472 (66.5)
Herpangina*	11 (10.0)[#]	160 (42.1)[##]	86 (39.1)	257 (36.2)
Streptococcal infection*	35 (31.8)[#]	181 (47.6)	130 (59.1)[##]	346 (48.7)
Influenza virus infection*	9 (8.2)[#]	85 (22.4)	51 (23.2)	145 (20.4)
Norovirus infection*	8 (7.3)[#]	79 (20.8)	58 (26.4)[##]	145 (20.4)
Rotavirus infection*	2 (1.8)[#]	30 (7.9)	23 (10.5)	55 (7.7)
RSV infection*	46 (41.8)[#]	260 (68.4)[##]	147 (66.8)	453 (63.8)
Mumps	10 (9.1)	28 (7.4)	22 (10.0)	60 (8.5)

Note: Values are presented as *n* (%) of facilities reporting at least one case within 1 year. * Infections showing a significant overall difference based on the chi-square test. [#] Significantly lower values based on residual analysis following the chi-square test (adjusted residuals < −1.96). [##] Significantly higher values based on residual analysis following the chi-square test (adjusted residuals > 1.96). *Abbreviation*: RSV, respiratory syncytial virus.

3.4. Regional analysis of infectious diseases

Table 4 shows regional distribution of facilities reporting infectious diseases (1-year facility-level reporting rates). COVID-19 infections were reported in over 90% of facilities across all regions. Reports of other infections varied, with adenovirus infection reported in 40–68% of facilities. Hand, foot, and mouth disease, herpangina, streptococcal, influenza virus, norovirus infection, rotavirus, RSV, and mumps infections were reported in 36–72%, 16–44%, 28–61%, 9–33%, 16–27%, 0–15%, 48–75%, and 2–12% of facilities, respectively. Significant regional differences in 1-year facility-level reporting rates were observed for adenovirus, hand, foot, and mouth disease, streptococcal, influenza virus, and rotavirus infections. Residual analysis identified significant deviations in 1-year facility-level reporting rates for adenovirus infections in Tohoku (adjusted residuals: −2.4), Kanto (adjusted residuals: −2.3), and Kyushu/Okinawa (adjusted residuals: 3.2). For hand, foot, and mouth disease, significant differences were observed in Kanto (adjusted residuals 2.0) and Shikoku (adjusted residuals −3.3). The residuals for streptococcal infections were significantly different in Tohoku (adjusted residuals −3.2), Shikoku (adjusted residuals −2.1), and Kyushu/Okinawa (adjusted residuals 2.3). The residuals for influenza infection were −2.4 for Tohoku, −2.2 for Hokuriku/Koshinetsu, and 3.4 for Kyushu/Okinawa. The adjusted residual for rotavirus infection was −3.2 for Kanto.

3.5. Population density–based analysis of infectious diseases

Table 5 shows a summary of the 1-year facility-level reporting rates for child-specific infectious diseases by population density category. COVID-19 infection was reported in over 95% of facilities across all density categories, with no significant differences observed. Adenovirus infection showed a non-linear association with population density, characterised by a peak at medium density. Hand, foot, and mouth disease exhibited a significant increase with higher population density. Influenza virus infection showed a complex pattern, with a medium-density peak and a significant linear trend. Rotavirus infection showed an inverse association with population density, with higher reporting rates in low-density areas and lower rates in high-density areas. RSV infection also exhibited a non-linear pattern, characterised by a medium-density trough. In contrast, herpangina, streptococcal infection, norovirus infection, and mumps were not significantly associated with population density.

4. Discussion

In this study, facility-level reporting rates of child-

Table 4. One-year facility-level reporting rates of child-specific infections by region (n = 710)

	Hokkaido	Tohoku	Kanto	Hokuriku/Koshinetsu	Tokai	Kinki	Chugoku	Shikoku	Kyushu/Okinawa	Total
COVID-19 infection	38 (97.4)	84 (97.7)	188 (96.9)	62 (100.0)	74 (97.4)	79 (91.9)	47 (94.0)	25 (100.0)	91 (98.9)	688 (96.9)
Adenovirus infection*	25 (64.1)	35 (40.7)$^{\#}$	89 (45.9)$^{\#}$	34 (54.8)	36 (47.4)	53 (61.6)	27 (54.0)	13 (52.0)	63 (68.5)$^{\#\#}$	375 (52.8)
Hand, foot, and mouth disease*	24 (61.5)	53 (61.6)	140 (72.2)$^{\#\#}$	40 (64.5)	51 (67.1)	60 (69.8)	30 (60.0)	9 (36.0)$^{\#}$	65 (70.7)	472 (66.5)
Herpangina	15 (38.5)	29 (33.7)	81 (41.8)	22 (35.5)	24 (31.6)	24 (27.9)	17 (34.0)	4 (16.0)	41 (44.6)	257 (36.2)
Streptococcal infection*	24 (61.5)	28 (32.6)$^{\#}$	99 (51.0)	34 (54.8)	38 (50.0)	42 (48.8)	19 (38.0)	7 (28.0)$^{\#}$	55 (59.8)$^{\#\#}$	346 (48.7)
Influenza virus infection*	8 (20.5)	9 (10.5)$^{\#}$	38 (19.6)	6 (9.7)$^{\#}$	14 (18.4)	24 (27.9)	10 (20.0)	5 (20.0)	31 (33.7)$^{\#\#}$	145 (20.4)
Norovirus infection	8 (20.5)	16 (18.6)	32 (16.5)	17 (27.4)	15 (19.7)	21 (24.4)	8 (16.0)	5 (20.0)	23 (25.0)	145 (20.4)
Rotavirus infection*	6 (15.4)	7 (8.1)	5 (2.6)$^{\#}$	8 (12.9)	8 (10.5)	6 (7.0)	5 (10.0)	0 (0.0)	10 (10.9)	55 (7.7)
RSV infection	27 (69.2)	58 (67.4)	120 (61.9)	42 (67.7)	57 (75.0)	56 (65.1)	25 (50.0)	12 (48.0)	56 (60.9)	453 (63.8)
Mumps	1 (2.6)	6 (7.0)	16 (8.2)	5 (8.1)	7 (9.2)	10 (11.6)	2 (4.0)	3 (12.0)	10 (10.9)	60 (8.5)

Note: Values are shown as the number of facilities (% reporting at least one case per year). * Represents infections that were significantly different based on the chi-square test. $^{\#}$ Indicates significantly low values (adjusted residuals < −1.96) based on residual analysis following a chi-square test. $^{\#\#}$ Indicates significantly high values (adjusted residuals > 1.96) based on residual analysis following a chi-square test. *Abbreviation:* RSV, respiratory syncytial virus.

Table 5. One-year facility-level reporting rates of child-specific infectious diseases by population density category (*n* = 710)

	Low density (*n* = 187)	Medium density (*n* = 167)	High density (*n* = 356)	Overall pattern
COVID-19 infection	184 (98.4)	163 (97.6)	341 (95.8)	No association
Adenovirus infection*	94 (50.3)	103 (61.7)##	178 (50.8)	Medium-density peak
Hand, foot, and mouth disease†	117 (62.6)	104 (62.3)	251 (70.5)##	Increase toward high density
Herpangina	66 (35.3)	62 (37.1)	129 (36.2)	No association
Streptococcal infection	86 (46.0)	81 (48.5)	179 (50.3)	No association
Influenza virus infection*†	23 (12.3)#	46 (27.5)##	76 (21.3)	Complex pattern (significant linear trend)
Norovirus infection	41 (21.9)	36 (21.6)	68 (19.1)	No association
Rotavirus infection*†	21 (11.2)##	15 (9.0)	19 (5.3)#	Inverse density association
RSV infection*	127 (67.9)	93 (55.7)#	233 (65.4)	Medium-density trough
Mumps	12 (6.4)	15 (9.0)	33 (9.3)	No association

Note: Values are shown as the number of facilities (% reporting at least one case per year). * Represents infections that were significantly different based on the chi-square test. † Represents infections with a significant linear trend based on the linear-by-linear association test. ## Indicates significantly high values (adjusted residuals > 1.96) based on residual analysis following a chi-square test. # Indicates significantly low values (adjusted residuals < −1.96) based on residual analysis following a chi-square test. *Abbreviation*: RSV, respiratory syncytial virus.

specific infectious diseases, including COVID-19, in kindergartens, daycare centres, and certified childcare centres across Japan, were examined with a particular focus on differences by facility type and regional context. The findings revealed significant differences in occurrence of infections by facility type and region, indicating that the burden of infectious diseases in childcare and early childhood education settings varied across institutional and local contexts during the COVID-19 pandemic.

4.1. Overall trends in child-specific infectious diseases during the COVID-19 pandemic

Notably, COVID-19 was reported in nearly all facilities, highlighting its pervasive impact across childcare environments. This widespread reporting is consistent with national surveillance data indicating that the survey period coincided with the sixth and seventh waves, during which a substantial proportion of reported COVID-19 cases occurred among children aged ≤ 10 years in Japan (*14*).

In contrast, other child-specific infectious diseases, such as influenza and norovirus, typically show regular seasonal epidemics during non-pandemic periods. Reportedly, substantial reductions in several seasonal infectious diseases occurred during the COVID-19 pandemic. Specifically, Sakamoto *et al*. reported that incidence of seasonal influenza was markedly lower than pre-pandemic levels (*15*), and Fukuda *et al.* observed significant declines in influenza and rotavirus gastroenteritis among hospitalised children (*3*). Similar reductions were also reported in other countries during periods when COVID-19 control measures were widely implemented (*16*). These findings cannot be directly compared with pre-pandemic facility-level data; however, they provide important context for interpreting relatively low reporting rates of child-specific infectious diseases observed in the present study.

4.2. Facility-type differences in child-specific infectious diseases

By facility type, kindergartens showed significantly lower 1-year facility-level reporting rates for several infections, including hand, foot, and mouth disease, herpangina, adenovirus, streptococcal infection, influenza virus, norovirus, rotavirus, and RSV, than daycare centres and/or certified childcare centres. Several child-specific infectious diseases are known to occur more frequently in younger children approximately 2 years of age than in older preschool children aged 5–6 years, including adenovirus infection (*17,18*), hand, foot, and mouth disease (*19,20*), herpangina (*21,22*), influenza virus infection (*23,24*), norovirus gastroenteritis (*25,26*), rotavirus gastroenteritis (*27,28*), and RSV infection (*29,30*). Reports show that immunological maturity increases with age and that younger children have limited immune responses to common pathogens, whereas older preschool children are more likely to have developed partial immunity through prior exposures (*31,32*).

In contrast, with regard to streptococcal infections, which typically peak around early school age, particularly at approximately 5 years of age, in the pre-pandemic period in Japan (*33*), the different age distribution observed in the present study suggests that age-specific differences may have influenced occurrence of infection, thereby affecting effectiveness of infection prevention measures during the COVID-19 pandemic.

This interpretation is further supported by age-related differences in the feasibility of infection prevention behaviours. Kindergarten-aged children can generally understand and practice basic infection prevention behaviours, such as hand hygiene and mask use, enabling preventive strategies to be directly implemented at the child level. However, younger children in daycare and certified childcare centres have limited ability to independently practice such behaviours; hence, preventive measures rely largely on caregivers, which

may have reduced their overall effectiveness.

Consistent with this explanation, it has been previously demonstrated that non-pharmaceutical interventions introduced to prevent COVID-19 transmission also led to substantial reductions in many other childhood infectious diseases (*16,34*). Collectively, lower reporting rates observed in kindergartens likely reflect a combination of age-related biological factors, including increasing immunological maturity and accumulated immunity, and greater feasibility of implementing infection prevention behaviours at the child level.

4.3. Regional variation in child-specific infectious diseases

Regarding regional variation in child-specific infectious diseases, initial comparisons indicated lower 1-year facility-level reporting rates in less densely populated regions, such as Shikoku, Tohoku, and Hokuriku/Koshinetsu, whereas higher reporting rates were observed in more urbanised regions, including Kanto and Kyushu/Okinawa. However, further analyses stratified by population density revealed heterogeneous and pathogen-specific patterns, indicating that regional variation in child-specific infectious diseases cannot be explained by population density alone.

Specifically, the reporting rates of hand, foot, and mouth disease increased with higher population density, consistent with previous epidemiological reports indicating that close contact in urbanised settings facilitates transmission (*20*). Influenza virus infection also showed a significant linear trend across population density categories, consistent with reports indicating that population concentration and human mobility contribute to influenza transmission (*23,34*).

Nevertheless, several infections, including herpangina, norovirus infection, and mumps, showed no clear association with population density. Streptococcal infection showed significant regional differences but did not show a linear association with population density. Furthermore, rotavirus infection was inversely associated with higher reporting rates in low-density areas, whereas adenovirus and RSV infections exhibited non-linear patterns. These heterogeneous findings are consistent with previous findings suggesting that paediatric infectious diseases occurrence is strongly influenced by age distribution, childcare attendance patterns, facility characteristics, and local infection control practices, rather than by population density alone (*28,29,34*).

Collectively, the present results indicate that regional differences in child-specific infectious disease occurrence reflect a complex interplay between population density and disease-specific epidemiological characteristics, underscoring the importance of considering pathogen-specific transmission dynamics when interpreting regional patterns.

4.4. Research Limitations

This study has some limitations. First, the survey response rate was relatively low (15.4%; valid response rate: 14.2%), which may limit the generalisability of the findings. Facilities with higher awareness of infection control or greater interest in infectious disease issues may have been more likely to respond, potentially introducing selection bias.

Second, the survey was conducted between January and April 2023, a period characterised by high COVID-19 prevalence among children in Japan. Heightened awareness, increased testing, and enhanced reporting practices during this period may have influenced facility-level reporting rates for COVID-19 and other child-specific infectious diseases. Therefore, reported rates may differ from those observed after May 2023, when COVID-19 was reclassified as a category 5 infectious disease in Japan.

Third, detailed information on socioeconomic factors, such as parental employment status, household income, or access to healthcare, was not collected, which may influence childcare facility selection and infection reporting practices. Furthermore, population density was used as a proxy measure for regional characteristics associated with infection transmission and may not fully capture local childcare environments, including facility size, class composition, staff-to-child ratios, or patterns of interaction among children. Substantial heterogeneity may also exist within the same population density category.

Accordingly, regional differences in child-specific infectious diseases should be interpreted with caution. In future studies, response rates should be increased to improve representativeness, for example, by providing participating facilities with feedback on study findings; more detailed facility-level and community-level indicators should be incorporated. In addition, longitudinal research is needed to examine how changes in COVID-19 classification and infection control practices influence occurrence and reporting of child-specific infectious diseases over time in childcare and early childhood education facilities.

5. Conclusions

This study provides empirical evidence on how facility type and regional context shape occurrence of child-specific infectious diseases during the COVID-19 pandemic in Japan by examining facility-level reporting rates across different childcare settings nationwide. Facility type showed a particularly strong association with infection occurrence, with kindergartens consistently exhibiting lower 1-year facility-level reporting rates across multiple child-specific infectious diseases. This finding integrates age-related differences, feasibility of infection prevention behaviours, and the

aforementioned pandemic-related non-pharmaceutical interventions. At the regional level, while initial comparisons suggested higher reporting rates in more urbanised areas, population-density-stratified analyses revealed heterogeneous and pathogen-specific patterns, highlighting the importance of disease-specific epidemiological characteristics.

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Latent classes of frailty and their association with intrinsic capacity in older cancer survivors: A study under the healthy aging paradigm

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Abstract: The aim of this study was to identify frailty profiles using latent class analysis (LCA) and examine their associations with intrinsic capacity (IC) among Chinese elderly cancer survivors. A total of 308 elderly cancer survivors were recruited from a tertiary hospital in Nantong, China between November 2023 and April 2024, and data were collected through questionnaires and clinical assessments. LCA was used to classify frailty subtypes, univariate analysis and multinomial logistic regression (reference: robust group) were used to identify associated factors, and one-way ANOVA was used to compare IC differences across subtypes. Three frailty profiles were identified—frail (31.5%), pre-frail (19.8%), and robust (48.7%)—with significant IC variations. Lower monthly household income (odds ratio (OR) = 16.00, $p = 0.028$), smoking (OR = 8.76, $p = 0.013$), malnutrition (OR = 5.25, $p = 0.044$), activities of daily living (ADL) (OR = 71.31, $p < 0.001$), depression (OR = 15.91, $p = 0.048$), and fatigue (OR = 33.43, $p < 0.001$) were independent risk factors. These findings indicate that Chinese elderly cancer survivors exhibit heterogeneous frailty profiles and that IC decline is positively associated with the severity of frailty. The identified risk factors and subtype characteristics provide a basis for devising tailored interventions to improve health outcomes in this population.

***Keywords*:** elderly cancer survivors, frailty, intrinsic capacity, latent class analysis, root cause analysis

1. Introduction

Currently, "healthy aging" has become a major issue of global public health concern. The data shows that China has the world's largest population of people age 65 and above (*1*). As a disease closely related to age, the incidence of cancer is significantly higher in the elderly population. By 2035, the incidence of newly diagnosed cancer among the elderly population over 65 years of age worldwide is estimated to reach as high as 60% (*2*). As forms and means of clinical treatment have advanced, the survival rate of cancer patients has risen. Therefore, the health and quality of life issues of cancer survivors after treatment have attracted widespread attention.

Frailty, as one of the research hotspots in the field of gerontology in recent years, refers to a clinical syndrome characterized by a decline in an individual's physiological reserves and resistance, rendering the body more susceptible to stressors and at a higher risk for adverse health outcomes (*3*). Cancer survivors, due to the complex impact of cancer itself as well as comprehensive treatments such as surgery and chemotherapy, experience a decline in physiological reserve, increased sensitivity to disease, and are more susceptible to the stimulation of the tumor itself and its treatment, thereby disrupting the body's balance and predisposing them to frailty (*4*). Moreover, the relationship between cancer and frailty may be attributed to their shared physiological mechanisms, such as reduced muscle mass and increased levels of inflammatory and cytokine factors (*5*). Among elderly cancer survivors, the incidence of frailty varies between 6% and 86%, with a median rate of 42% (*6*). In fact, over half of elderly cancer survivors are pre-frail or frail, leading to increased dependency, reduced treatment tolerance, and increased risks of postoperative complications, disease progression, and mortality (*7*). This significantly hampers patients' quality of life and increases readmission rates and medical costs, imposing a heavy burden of care on families and society.

To address the growing burden of frailty and care dependency among older cancer survivors, the World Health Organization (WHO) has proposed an innovative approach — Integrated Care for Older People (ICOPE). Within this framework, optimizing intrinsic capacity (IC)

is central to promoting healthy aging and reducing care dependency (*8*). Multiple studies have confirmed that the onset of frailty is closely associated with a decline in an individual's IC, and enhancing IC represents a core strategy for frailty prevention (*9*). The WHO defines IC as the composite of all an individual's physical and mental capacities, encompassing the domains of locomotion, vitality, cognition, psychology, and sensory function (*10*). This metric comprehensively reflects the overall physiological reserve of the organism, and its trajectory serves as a key predictor of frailty onset. Therefore, in the holistic management of older cancer patients, early identification, continuous monitoring, and proactive intervention in IC decline are essential. These measures not only help predict the risk of frailty but also form the core pathway for intervening in and ameliorating frailty, enhancing functional ability, and ultimately achieving the goal of "healthy aging".

Moreover, researchers universally agree that frailty represents a dynamic state that causes individuals to suffer losses in one or more functional domains (physiological, psychological, or social) and increases the risk of adverse outcomes. It is potentially reversible and preventable in the early stages (*11-13*). This reversibility underscores the need to prioritize frailty prevention and management in cancer care. Indeed, frailty screening is increasingly used for risk stratification in elderly cancer survivors to predict surgical prognosis and chemotherapy toxicity (*14*), making early identification and targeted intervention critical. However, effective intervention relies on accurate assessment, which currently faces a key limitation. While no consensus exists on a universal definition, the most widely used tool is Fried's frailty phenotype, which defines frailty by five criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity (*15*). However, most existing studies use scale scores as the criterion for frailty assessment, potentially overlooking the individual differences and diversity within the population.

Latent class analysis (LCA) is a probabilistic model-based approach that effectively identifies homogeneous subgroups within heterogeneous populations by clustering individuals based on similar observed characteristics (*16*). Its utility in uncovering the heterogeneity of frailty is well-supported by existing research. For instance, LCA has been used to identify distinct physical frailty subgroups with varying severity among older US nursing home residents (*17*). Similarly, studies of community-dwelling adults have revealed diverse risk profiles, such as "relatively healthy", "malnourished", and "cognitively or mood-impaired" classes (*18*). These findings collectively demonstrate that LCA is a robust method for delineating heterogeneous frailty phenotypes in older populations. Despite this established methodological utility, its application to the specific population of elderly cancer survivors remains limited. In particular, there is a paucity of research examining how the distinct frailty categories identified *via* LCA are associated with IC in this vulnerable group.

To address this gap, the current study uses LCA to classify frailty in elderly cancer survivors, it investigates the differences in influencing factors, and it explores the relationship between different frailty categories and IC. These findings will assist healthcare providers in formulating targeted interventions to alleviate frailty and improve IC in elderly cancer survivors.

2. Patients and Methods

2.1. Study design and participants

Convenience sampling was used to recruit 308 cancer patients from a Grade A tertiary hospital in Nantong, Jiangsu Province between November 2023 to April 2024. Inclusion criteria included being age 60 years or older; having a histological or cytological diagnosis of malignant tumors; being able to ambulate independently with or without assistance; and providing informed consent for voluntary participation. Exclusion criteria consisted of having hearing or speech impairments and communication challenges; cognitive impairment, mental illness; and the inability of patients with other serious illnesses to cooperate with investigation. The formula used for sample size estimation was $n = Z^2 \alpha/2[P(1-P)]/\delta^2$, with a significance level of $\alpha = 0.05$ and a two-tailed $Z\alpha/2$ value of 1.96. The estimated value of the expected incidence was set at 42% (*6*), based on the combined frailty rate of elderly cancer survivors from previous systematic reviews. Given the higher incidence of frailty in elderly hospitalized cancer patients, a δ of $\pm$ 10% was chosen for this study. The sample size was estimated to be 94, with a final sample size of 118 determined after accounting for a 20% non-response rate.

2.2. Research instruments

2.2.1. Demographic and disease characterization questionnaire

A general information survey form, developed collaboratively by the research team based on a review of relevant literature, included demographic information such as sex, age, marital status, level of education, average monthly family income, smoking, drinking alcohol, comorbidities, and disease-related data including cancer site and cancer staging.

2.2.2. Fried phenotype (FP)

The FP was developed by Fried *et al.* (*15*) and is used to assess the frailty status of elderly individuals. There are five diagnostic criteria: *i*) Weight loss: A weight loss of 4.5 kg in the past 12 months, *ii*) Self-reported exhaustion:

Asking the patient if he or she feels that everything he or she does requires effort and if this feeling has occurred for more than 3 days in the past week, *iii*) Low physical activity: A "yes" answer to either of the following questions indicates low physical activity: having limitations in performing certain activities of daily living due to physical reasons; in the past month, being able to complete only part of what one intended to do in daily activities due to physical reasons, *iv*) Slow gait speed: Measuring the time taken for the patient to walk 4.5 meters. If the time taken by a male (height ≤ 173 cm) or female (height ≤ 159 cm) is > 7 seconds or if the time taken by a male (height > 173 cm) or female (height > 159 cm) is > 6 seconds, this indicates slow gait speed, *v*) Weak grip strength: Using a grip strength meter to measure the maximum grip strength of the dominant hand of elderly individuals. Grip strength values are stratified by sex and BMI, and if the individual's grip strength value is lower than the grip strength cutoff value corresponding to his or her BMI, it indicates decreased grip strength. Meeting 1-2 criteria indicates pre-frailty, meeting 3 or more criteria indicates frailty, and not meeting the above criteria indicates non-frailty.

2.2.3. IC

Based on the five key domains of IC proposed by the WHO and its recommended assessment tools, our research team collectively developed an IC assessment instrument and methodology covering the following five domains (*19,20*):

i) Locomotor capacity: This was evaluated using the Short Physical Performance Battery (SPPB) developed by Guralnik *et al.*. This scale includes three tests: a balance test (3 items), a gait speed test, and a chair stand test. For the balance test, items 1 and 2 are scored 0–1 point each, while item 3 is scored 0–2 points; both the gait speed test and chair stand test are scored 0–4 points each. The total score ranges from 0 to 12, with higher scores indicating better locomotor capacity.

ii) Sensory function: Sensory function decline was defined as self-reported visual or hearing impairment that affects daily life.

iii) Vitality: The Short-form Mini Nutritional Assessment (MNA-SF) was used to assess the nutritional status of participants. It includes six items—appetite, body weight, activity, acute illness, neuro-psychological issues, and BMI—with a total score of 14 points. A lower score indicates poorer nutritional status, and a score of < 11 points is considered malnutrition.

iv) Psychological function: The Geriatric Depression Scale (GDS) was used to evaluate the depression status of participants. It consists of 15 items with a total score of 15 points. A higher score indicates more severe depressive symptoms, and a score of ≥ 5 points is considered indicative of depression.

v) Cognitive function: A Chinese version of the Mini-Mental State Examination (MMSE) that was developed by Folstein *et al.* was created by Chinese researcher Xiaoxuan Zhou. It includes 30 items covering orientation, immediate memory, and calculation, with 1 point awarded for each correct answer and 0 points for incorrect answers. The total score ranges from 0 to 30, with higher scores indicating better cognitive function. In this study, each of the five domains of IC was dichotomized: a score of 0 indicated decline in that domain, and 1 indicated normal function. The total IC score ranged from 0 to 5, with a score of ≤ 4 defined as overall IC decline; lower total scores indicated more severe IC impairment.

2.2.4. Cancer Fatigue Scale (CFS)

The CFS was developed by Okuyama *et al.* (*21*) and is used to assess the fatigue status of cancer patients. It includes three dimensions—physical, emotional, and cognitive—with a total of 15 items and a score ranging from 0–60 points. A higher score indicates more severe fatigue, and a score of ≥ 18 points is defined as fatigue.

2.2.5. Instrumental Activities of Daily Living Scale (IADL)

The IADL includes eight items such as cooking, housekeeping, laundry, medication management, transportation use, shopping, financial management, and phone use, with a total score of 16 points (*22*). If a patient needs assistance with one item, he or she is considered to have an IADL disability. A lower score indicates lesser ability to perform activities of daily living.

2.3. Data collection

Somatic measurements were obtained by a trained professional, while the questionnaire survey was administered with standardized instructions that outlined the study's objectives and importance. Participants were required to provide informed consent by signing a consent form prior to participation. In cases where participants had difficulty completing the questionnaire, the researcher assisted in completing the form without using leading language to ensure an unbiased and comprehensive recording of responses. Upon receipt of the questionnaire, a thorough assessment of its completeness was promptly conducted. Any missing items or omissions were promptly identified and participants were requested to provide the necessary information to supplement their responses.

2.4. Data analyses

The software Mplus 8.3 was used to perform a LCA on frailty. The fit indices mainly included: *i*) the Akaike Information Criterion (AIC), the Bayesian Information

Criterion (BIC), and the adjusted Bayesian Information Criterion (aBIC). Smaller values for these three statistical indices indicate better model fit, *ii*) Entropy was used to evaluate the accuracy of the model, with values ranging from 0 to 1. A value closer to 1 indicates a more precise model fit, and *iii*) Significant values ($p < 0.05$) for the Lo-Mendell-Rubin likelihood ratio test (LMRT) and bootstrap likelihood ratio test (BLRT) indicated that the k-class model fit better than the (k-1)-class model.

Data were analyzed using SPSS 26.0, with categorical data expressed as frequencies and percentages and continuous data expressed as the mean ± standard deviation ($\bar{x} \pm s$). Between-group comparisons were performed using χ^2 tests or Fisher's exact probability test and analysis of variance. Multiple logistic regression analysis was used to explore the factors influencing frailty subtypes. Finally, one-way analysis of variance was used to compare differences in IC among different frailty classes. The significance level was set at $\alpha = 0.05$.

2.5. Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Affiliated Hospital of Nantong University (2023-K141-01). All participants in this study provided signed informed consent and willingly took part in this study.

3. Results

The Harman single-factor test was used to assess common method bias (*23*). Findings revealed that the characteristic roots of the seven factors surpassed 1, elucidating 57.35% of the overall variance, with the predominant factor representing 19.69%, falling below the threshold of 40%. Consequently, one can plausibly conclude that there is no pronounced common method bias in this study.

3.1. Participant characteristics

A total of 315 survey questionnaires were distributed in this study, with 308 valid responses returned, resulting in a valid response rate of 97.8%. Among the 308 cancer patients, the average age was 69.38 ± 6.26 years, with 203 males (66.1%) and 104 females (33.9%). In terms of their level of education, 140 participants had a primary school education or below (39.7%), while 168 had at least a junior high school education (47.6%). Additional information can be found in Table 1.

3.2. Classification of the latent profile

LCA was performed using five frailty-related items. Models with varying numbers of classes ranging from 1 to 5 were generated, and the fit of each model is shown in Table 2. As the number of classes increased, values for the AIC decreased, with the 3-class model exhibiting the highest entropy value. However, beyond the 3-class model, values for the AIC, BIC, and aBIC increased with each additional class. The statistical tests for model 4 (BLRT) and model 5 (LMRT and BLRT) did not yield significant results ($p > 0.05$). After conducting a thorough evaluation of the fit indices for each model, model 3 was determined to be the most suitable latent class model.

The data shown in Table 3 demonstrates that the average probability of categorization for elderly cancer survivors ranged from 95.6% to 99.5%, exceeding the threshold of 95%. This suggests that the outcomes derived from the optimal model utilized in this study to analyze potential categories were dependable and exhibited strong discriminatory capability.

3.3. Features and names of each latent profile

The latent class conditional probability plot for the three categories of elderly cancer survivors across five external indices is shown in Figure 1. C1 group exhibits a relatively high probability across all five external indices, indicating that this group of elderly cancer survivors displays significant signs of frailty in multiple aspects. Specifically, they may have experienced notable weight loss, frequently feel extreme exhaustion, engage in low levels of daily physical activity, have a noticeably slower gait, and possess weaker grip strength. The combination of these characteristics led to the classification of the C1 group as the "frail group".

The C2 group exhibit performance on the five external indices that fell between the C1 and C3 groups. Specifically, the C2 group exhibited a moderate to high conditional probability for certain indices, particularly in terms of self-reported exhaustion and slow gait speed, indicating a certain degree of frailty risk in these areas. However, compared to the C1 group, patients in the C2 group performed relatively better on other indices, without displaying the widespread frailty signs seen in the C1 group. Therefore, the C2 group was classified as the "pre-frail group", meaning that while they exhibit some frailty characteristics, they have not reached the level of comprehensive frailty observed in the C1 group.

In contrast to the C1 group, the C3 group exhibited a lower probability across the five external indices, indicating that this group of elderly cancer survivors is generally in better condition without obvious signs of frailty. They likely maintain an appropriate weight, report less fatigue, engage in higher levels of physical activity, have a steady gait, and possess stronger grip strength. Based on these characteristics, the C3 group has been designated as the "robust group". The class membership probability was 31.5% ($n = 97$) for "frail group", 19.8% ($n = 61$) for "pre-frail group", and 48.7% ($n = 150$) for the "robust group".

Table 1. Comparison of frailty in groups with different characteristics

Variables	Robust group *n* (%)	Frail group *n* (%)	Pre-frail group *n* (%)	Statistics	*P*
Sex				14.884*	0.001
Male	19 (18.3)	65 (62.5)	20 (19.2)		
Female	78 (38.2)	85 (41.7)	41 (20.1)		
Age				10.212**	0.111
60–69	51 (38.1)	54 (40.3)	54 (40.3)		
70–79	38 (27.1)	79 (56.4)	23 (16.4)		
80–89	8 (26.7)	14 (46.7)	14 (46.7)		
90~	0	3 (75.0)	3 (75.0)		
Marital status				5.546*	0.062
Single	3 (12.5)	13 (54.2)	8 (33.3)		
Cohabitation	94 (33.1)	137 (48.2)	53 (18.7)		
Level of education				15.464*	< 0.001
Primary school and below	28 (20.0)	77 (55.4)	34 (24.5)		
Junior high school and above	69 (41.1)	73 (43.2)	27 (16.0)		
Monthly family income (RMB)				31.823*	< 0.001
< 3000	3 (11.5)	18 (12.7)	5 (19.2)		
3000–5000	23 (40.3)	75 (62.3)	30 (23.4)		
> 5000	71 (48.5)	57 (75.0)	26 (16.9)		
Living alone				2.931**	0.289
Yes	3 (50.0)	1 (16.7)	2 (33.3)		
No	94 (31.1)	149 (49.3)	59 (19.5)		
Smoking				21.993*	< 0.001
No	32 (20.5)	95 (60.9)	29 (18.6)		
Yes	65 (42.8)	55 (36.2)	32 (21.1)		
Drinking alcohol				13.181*	< 0.001
No	34 (22.2)	88 (57.5)	31 (20.3)		
Yes	63 (40.6)	62 (40.0)	30 (40.6)		
Malnutrition				61.859*	< 0.001
No	92 (41.6)	77 (34.8)	52 (23.5)		
Yes	5 (5.7)	73 (83.9)	9 (10.3)		
Comorbidity				9.563**	0.119
0	56 (35.4)	72 (45.6)	30 (19.0)		
1	34 (32.7)	48 (46.2)	22 (21.2)		
2	7 (17.1)	25 (61.0)	9 (22.0)		
≥ 3	0 (0)	5 (100.0)	0 (0)		
Polypharmacy				5.515	0.063
≥ 5	4 (18.2)	16 (72.7)	2 (9.1)		
< 5	93 (32.5)	134 (46.9)	59 (20.6)		
Cancer site				22.170*	0.005
Upper GI	26 (39.4)	32 (47.8)	8 (12.1)		
Lower GI	15 (33.3)	22 (48.9)	8 (17.8)		
Breast	27 (37.5)	26 (36.1)	19 (26.4)		
Liver	6 (12.2)	36 (73.5)	7 (14.3)		
Other	23 (30.3)	34 (44.7)	19 (25.0)		
Cancer stage				11.744*	0.003
I-II	60 (38.0)	62 (39.2)	36 (22.8)		
III-IV	37 (24.7)	88 (58.7)	25 (16.7)		
ADL				204.662*	< 0.001
normal	94 (60.3)	14 (76.0)	48 (30.8)		
disability	3 (2.0)	136 (74.0)	13 (30.1)		
Fatigue				184.933*	< 0.001
No	86 (58.5)	9 (6.5)	44 (31.7)		
Yes	11 (6.8)	141 (83.4)	17 (10.1)		
Depression				55.790*	< 0.001
No	96 (38.7)	95 (38.3)	57 (23.0)		
Yes	1 (1.7)	55 (91.7)	4 (6.7)		

*χ^2; **Fisher's exact probability method.

3.4. Univariate analysis of frailty latent profiles in elderly cancer survivors

Univariate analysis revealed significant differences among the three groups in terms of sex, level of education, average monthly household income, smoking, drinking alcohol, malnutrition, ADL, cancer site, cancer stage, fatigue, and depression ($p < 0.05$), as shown in Table 1.

A multifactorial analysis was performed to examine

Table 2. Fit indices for each model

Model	AIC	BIC	aBIC	Entropy	*p* (LMRT)	*p* (BLRT)	Categorical probability
1	2082.512	2101.163	2085.305				
2	1637.603	1678.634	1643.747	0.913	0.0000	0.0000	0.506/0.494
3	1635.420	1698.831	1644.914	0.940	0.0025	0.0300	0.314/0.198/0.487
4	1635.864	1721.656	1648.710	0.855	0.0286	0.4286	0.302/0.014/0.208/0.471
5	1643.659	1751.832	1659.856	0.926	0.4142	0.6667	0.266/0.432/0.026/0.208/0.068

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; aBIC, Adjusted Bayesian Information Criterion; LMRT, Lo-Men-dell-Rubin likelihood ratio test; BLRT, Bootstrapped likelihood ratio test.

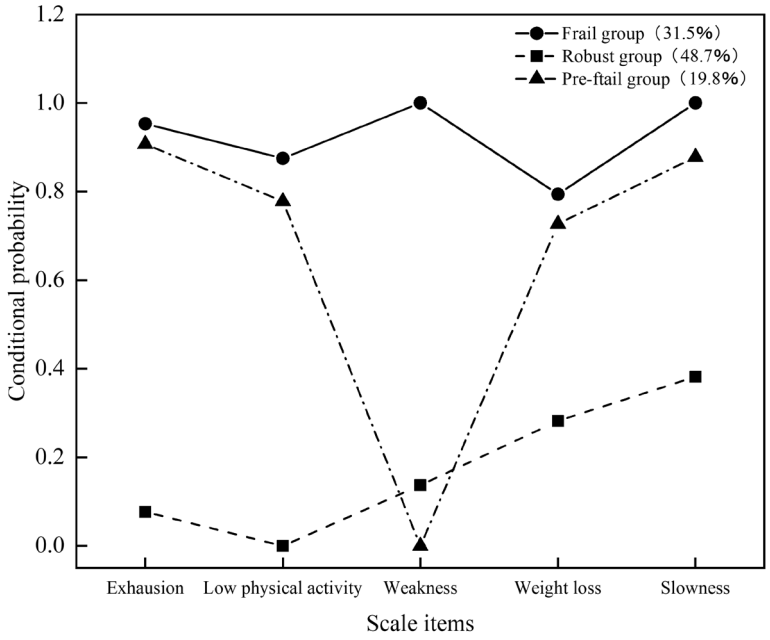

Figure 1. Latent profiles of frailty among elderly cancer survivors.

Table 3. The probability of latent profile analysis

Profile	1	2	3
1	0.995	0.000	0.005
2	0.000	0.956	0.044
3	0.002	0.029	0.968

potential categories of weakness in elderly cancer survivors as shown in Table 4. The statistically significant single-factor variables including sex, level of education, monthly household income, smoking, drinking alcohol, malnutrition, low ADL, cancer site, cancer stage, fatigue, and depression were included as categorical variables, with the last category serving as the reference. Using the three latent classes of frailty as dependent variables and the robust group as the reference group, multivariate logistic regression analysis was performed.

Specifically, an individual with a monthly household income below 3,000 RMB (frail group: odds ratio (OR) = 16.000, 95% confidence interval (CI) [1.343, 190.617]) was more likely to be in the frail group compared to individuals in the robust group. Moreover, an individual with a monthly household income ranging from 3000 to 50,000 RMB (frail group: OR = 4.278, 95% CI [1.221, 14.988]; pre-frail group: OR = 3.392, 95% CI [1.439, 7.997]) was more likely to be in the frail group or pre-frail group. Similarly, an individual who smoked (frail group: OR = 8.757, 95% CI [1.579, 48.553]), was malnourished (frail group: OR = 5.252, 95% CI [1.043, 26.459]), had fatigue (frail group: OR = 33.433, 95% CI [7.662, 145.882]), or had depression (frail group: OR =15.907, 95% CI [1.025, 246.960]) was more likely to be in the frail group. Additionally, an individual with low ADL (frail group: OR = 71.313, 95% CI [13.715, 370.802]); pre-frail group: OR = 5.747, 95% CI [1.246, 26.509]) was more likely to be in the frail group or pre-frail group.

3.5. Comparison of IC among patients with different latent classes of frailty

In this study, the proportion of patients with IC decline was 79.5%. Comparisons of IC across the three latent classes are shown in Table 5.

4. Discussion

Using LCA to categorize frailty in this population, the study reveals distinct classification characteristics of

Table 4. Multiple logistic regression on subtypes of frailty

Variables		"Frail group"				"Pre-frail group"			
		β	OR	95% CI	*p*	*β*	OR	95% CI	*p*
Sex	Male, Ref.: Female	0.584	1.793	0.346–9.289	0.486	0.245	1.278	0.409–3.989	0.673
Monthly household income	< 3,000, Ref.: > 5,000	2.773	16.000	1.343–190.617	0.028	1.581	4.858	0.900–26.224	0.066
	3,000-5,000, Ref.: > 5,000	1.453	4.278	1.221–14.988	0.023	1.222	3.392	1.439–7.997	0.005
Level of education	Primary and below, Ref.: Middle school and above	-0.291	0.748	0.206–2.714	0.659	0.798	2.222	0.988–5.000	0.054
Cancer site	Upper GI, Ref.: Other	-0.364	0.695	0.143–3.369	0.651	-1.116	0.328	0.101–1.061	0.063
	Lower GI, Ref.: Other	0.957	2.604	0.402–16.863	0.315	-0.088	0.916	0.261–3.212	0.891
	Breast cancer, Ref.: Other	1.116	3.053	0.584–15.978	0.186	0.264	1.303	0.484–3.508	0.601
	Lung cancer, Ref.: Other	1.489	4.432	0.529–37.097	0.170	0.508	1.662	0.349–7.910	0.523
Cancer stage	I-II, Ref.: III-IV	0.719	2.052	0.422–9.981	0.373	0.031	1.031	0.325–3.274	0.959
Smoking	Yes, Ref.: No	2.170	8.757	1.579–48.553	0.013	0.556	1.744	0.591–5.141	0.314
Drinking alcohol	Yes, Ref.: No	1.088	2.969	0.612–14.411	0.177	0.556	1.744	0.591–5.141	0.314
Malnutrition	Yes, Ref.: No	1.659	5.252	1.043–26.459	0.044	0.518	1.679	0.388–7.263	0.488
Low ADL	Yes, Ref.: No	4.267	71.313	13.715–370.802	< 0.001	1.749	5.747	1.246–26.509	0.025
Fatigue	Yes, Ref.: No	3.510	33.433	7.662–145.882	< 0.001	0.596	1.815	0.593–5.553	0.296
Depression	Yes, Ref.: No	2.767	15.907	1.025–246.960	0.048	1.754	5.777	0.425–78.516	0.188

frailty scores, delineating three potential subtypes. The "frail group" accounted for 31.5% (97/308), the "pre-frail group" accounted for 19.8% (61/308), and the "robust group" accounted for 48.7% (150/308). Multiple fit indices demonstrated the strong fit of the model, revealing distinctions among potential categories of frailty in elderly cancer survivors and reflecting the diversity of frailty within this population, which is consistent with findings from a previous study (*24*). Based on scale scoring criteria, elderly cancer survivors in the "robust group" exhibited lower scores across all items, indicating that these patients remain in good physical and mental condition despite cancer stress and are less affected by the disease. Conversely, patients in the "frail group" exhibited elevated scores across all measured parameters, making them the key population that requires focused intervention. In addition, individuals in the "pre-frail group" had moderate scores overall, yet they did have a markedly higher score for "exhaustion" and "slowness" in particular, suggesting diminished physical capacity and a heightened perception of fatigue in this population. Hence, healthcare personnel need to recognize the differences in care requirements across patient demographics, they need to more thoroughly evaluate frailty indices in elderly cancer survivors, and they need to incorporate resources and interventions into care strategies to mitigate and delay the onset and progression of frailty.

An analysis of the demographic characteristics of frail elderly cancer survivors can assist healthcare personnel in promptly identifying patients across various categories and offering tailored guidance and interventions. The findings of this study indicate significant variability in average monthly household income and smoking status among elderly cancer survivors categorized as frail ($p < 0.05$). Zhang *et al.* found that non-frail elderly individuals have higher household incomes compared to frail elderly individuals (*25*). The combination of cancer and frailty results in increased medical costs and the need for prolonged care, further compounding the economic strain on patients. This heightened financial burden may hamper patients' compliance with treatment regimens, exacerbate the progression of frailty, and perpetuate a detrimental cycle of deteriorating health. Additionally, a previous smoking habit has been identified as a factor contributing to frailty in elderly individuals with cancer, which is consistent with the study by Shewa *et al.* (*26*). Smoking is a major risk factor for cancer development, and it is associated with 20 to 30% of cancer cases (*27*). Prolonged smoking has been linked to the exacerbation of cancer-related complications (*28*). The harmful substances present in cigarettes have the potential to elevate inflammatory markers, ultimately resulting in a deterioration of overall health and muscle wasting (*29*). Therefore, healthcare personnel should conduct comprehensive health education on smoking cessation, explain the harmful effects of smoking to the body to

Table 5. Comparison of intrinsic capacity scores among different frailty classes in elderly cancer survivors

Group	Number	IC
Frail group	97	3.44 ± 0.61
Pre-frail group	61	3.56 ± 0.67
Robust group	150	4.02 ± 0.87
F*		19.347
p		< 0.05

*F: One-way ANOVA.

patients who have not quit smoking, and provide diverse, comprehensive, and effective smoking cessation support to increase the success rate of smoking cessation and prevent or alleviate the onset and progression of frailty.

In addition, regression analysis indicated that elderly cancer survivors with malnutrition are more likely to be classified in the "frail group", which is consistent with existing evidence (*30,31*). Malnutrition plays a crucial role in the pathophysiology of frailty (*32*). In cancer patients, the tumor itself, adverse effects of treatment, and cachexia reduce appetite and nutrient intake while increasing catabolism (*30,33*), leading to protein insufficiency. This drives muscle loss, reduced physiological reserve, and a heightened risk of frailty (*34*). Additionally, adverse outcomes of malnutrition, such as osteoporosis, sarcopenia, cognitive impairment, and falls, all contribute to the progression of frailty. The European Society for Clinical Nutrition and Metabolism recommends oral nutritional supplements (ONS) as a first-line intervention, combined with exercise (*35*). The Mediterranean diet is recognized as a suitable dietary regimen for addressing frailty in accordance with international guidelines (*36*). This diet can reduce the levels of inflammatory mediators in the body, thereby reducing the likelihood of frailty (*37*). Consequently, early evaluation of the risk of malnutrition in cancer patients is recommended for the future. A thorough assessment, which includes the measurement of body composition and resting energy expenditure, should be performed. For those at risk, adopting the Mediterranean diet or some other anti-inflammatory diet may help to mitigate metabolic stress and inflammation.

Moreover, these findings indicate that elderly cancer survivors with depression have a higher likelihood of being classified in the "frail group", which is consistent with the findings of Gilmore *et al.* (*38*). Notably, depression and frailty share overlapping mechanisms and neurobiological features (*39*). Depressive symptoms correlate with elevated inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), which promote neurohormone-mediated muscle protein catabolism. This leads to sarcopenia, metabolic dysfunction, and impaired resilience, collectively driving frailty (*40*). Additionally, depression induces mitochondrial dysfunction in metabolically vulnerable dopaminergic neurons, reducing ATP synthesis. The resulting decline in dopaminergic tone contributes to apathy, reduced mobility, and accelerated functional decline, thereby exacerbating frailty (*41*). Healthcare personnel should incorporate depression screening in frailty assessments for elderly cancer survivors, promptly identify depressive symptoms, and offer psychological support to alleviate negative emotions, alleviate depression, and mitigate the progression of both frailty and depression.

In addition, findings indicated that elderly cancer survivors experiencing fatigue are more likely to be categorized in the "frail group", which aligns with the study by Tohi *et al.* (*42*). The main reason why is that cancer patients experience a high degree of physical fatigue, which leads to decreased exercise tolerance, feelings of exhaustion, and impaired daily functioning, indirectly resulting in the onset of frailty (*43*). Moreover, the long-term presence of chronic fatigue can cause negative emotions such as anxiety and depression in patients, interfering with treatment compliance and reducing quality of life, thereby exacerbating frailty (*44*). Consequently, healthcare personnel should add to their understanding of cancer-related fatigue, recognizing its multifaceted and enduring nature, and enhance patients' quality of life. Additionally, various forms of peer support activities can facilitate mutual sharing and stress relief among patients, helping them build confidence in overcoming the disease, encouraging more active coping strategies for cancer-related fatigue, and ultimately delaying frailty.

The findings of this study indicate that elderly cancer survivors with lower levels of ADL are more likely to be classified into the "frail group", which is in line with the conclusions reached by Pu *et al.* (*45*). Additionally, Yuan *et al.* highlighted the significance of impairments in daily activities and balance issues in the identification of frailty among the elderly (*46*). The primary reason why is that patients' long-term reduction in independent activities leads to muscle atrophy, and the progressive loss of skeletal muscle mass and function increases the risk of frailty (*45*). Moreover, patients with less ability to perform ADLs often suffer from compromised personal health, dysfunction, or limited mobility, resulting in reduced social activities, disrupted social networks, and decreased social participation, which can easily lead to feelings of loneliness (*47*). A study has found that social isolation and loneliness are closely related to frailty (*48*). Therefore, nurses should develop individualized nursing plans based on the ADLs of elderly cancer survivors, such as encouraging them to continue engaging in daily exercise within their capabilities, exposing them to new things, encouraging them to actively participate in social activities, and encouraging them to build up their social networks, in order to delay the decline of physical function and the progression of frailty.

The results of this study indicated that 79.5% of elderly cancer survivors exhibited IC decline, a

proportion consistent with findings from a previous study (*49*). This indicates that IC impairment in elderly cancer survivors is a pressing issue that cannot be ignored. Additionally, significant differences in IC were observed among the three frailty subtypes ($p < 0.05$), suggesting a close association between IC and frailty severity in elderly cancer survivors, which is in line with the findings of Ntsama *et al.* (*8*). Existing research has confirmed that impairments in all IC domains including sensory function, psychosocial function, locomotor capacity, cognitive function, and vitality are correlated with frailty (*50*). The underlying mechanism may be explained as follows: elderly patients with frailty already have reduced physiological reserves and an elevated risk of physiological function decline. As a persistent stressor, cancer can further diminish their physiological function, thereby exacerbating IC impairment. These findings highlight the need for healthcare personnel to develop targeted interventions to enhance IC, delay the progression of frailty, and ultimately improve patients' health outcomes.

Nevertheless, this study had several limitations. Firstly, this study used convenience sampling, resulting in a lack of representativeness in the sample and causing selection bias. Second, this study is a small-scale, single-center cross-sectional survey with limited sample representativeness. The method of classification used in the study relies on the characteristics of the current sample and the specific assessment tools used, precluding detailed classification for all patients. This may lead to limitations in the method of classification, thereby restricting the general applicability of the study's findings. In future studies, we plan to expand the sample size and adopt widely recognized assessment tools for patient classification. Moreover, we intend to conduct additional research to validate the applicability of these methods of classification in different patient populations. Third, this study examined the correlation between different variables and frailty only in a cross-sectional fashion, failing to track the causal link between variables and frailty over time. Therefore, future research should aim to increase the sample size through systematic sampling, conduct multi-center longitudinal studies to understand the trajectory of changes in frailty among elderly cancer survivors, and provide a basis for precise interventions. Finally, the wide confidence intervals for some strong predictors indicate imprecision in the effect size estimates, which was likely due to the sample size and skewed distribution of these factors. While confirming their importance, future larger-scale studies need to quantify these associations more precisely.

5. Conclusion

Elderly cancer survivors have a high incidence of frailty and exhibit heterogeneity. Here, they were classified into three categories, namely a "frail group", a "pre-frail group", and a "robust group", based on LCA. Through careful classification of frail patients, we can gain a more precise understanding of the frailty characteristics of different patient groups. Potential categorical factors, such as monthly household income, smoking, fatigue, depression, malnutrition, and low ADL, heighten the risk of elderly cancer survivors becoming frail. These findings provide a theoretical basis for healthcare personnel to regularly assess the risk of frailty, identify high-risk groups, and develop patient-centered interventions. Moreover, there were differences in IC among patients in different classes. These findings provide a basis for healthcare personnel to regularly assess the risk of frailty, identify high-risk groups with reduced IC, and thereby alleviate frailty and improve IC levels in those groups.

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Investigating the link between Japanese Anticholinergic Risk Scale and laxative prescription in older adults: A cross-sectional study of 9,838 patients using dispensing claims from community pharmacies

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Abstract: Anticholinergic medications can cause constipation in older adults. The Japanese Anticholinergic Risk Scale (JARS), released in May 2024, is not yet sufficiently validated clinically. We examined the association between total anticholinergic burden based on JARS and laxative prescriptions. This cross-sectional study utilized community pharmacy dispensing claims for outpatients aged ≥ 65 years who were registered with a family pharmacist between November 1 and December 31, 2024. Chronic medication use was defined as prescriptions totaling ≥ 28 days during the study period. The primary analysis focused on patients receiving 5–9 concomitant chronic medications. Among the 9,838 patients (mean age 81.1 ± 7.3 years; 61.1% female), 39.4%, 33.2%, 14.7%, 7.0%, 3.1%, and 2.5% demonstrated JARS scores of 0, 1, 2, 3, 4, and ≥ 5, respectively. Compared with JARS = 0, adjusted odds ratios (aORs) for laxative prescriptions were 0.85 (95% confidence interval [CI]: 0.76–0.94, $p = 0.003$) for JARS = 1; 0.79 (0.69–0.91, $p = 0.001$) for JARS = 2; 0.94 (0.79–1.13, $p = 0.537$) for JARS = 3; 1.20 (0.93–1.55, $p = 0.153$) for JARS = 4; and 1.64 (1.24–2.16, $p < 0.001$) for JARS ≥ 5. This indicated a stepwise pattern with positive association at the highest burden. Furthermore, use of a drug rated 3 on the JARS revealed association with higher odds of laxative prescription (aOR: 1.71, 95% CI: 1.38–2.12, $p < 0.001$). Both a total JARS burden ≥ 5 and drugs rated 3 on the JARS were significantly associated with laxative prescribing.

***Keywords*:** anticholinergic burden, community pharmacists, constipation, JARS, chronic medication

1. Introduction

Anticholinergic medications have a major safety implication in older adults because of their association with cognitive impairment, urinary retention, dry mouth, and constipation. Additionally, age-related pharmacokinetic changes and polypharmacy may further exacerbate these risks (*1,2*).

Constipation is common among older adults, and it negatively affects their quality of life (*3,4*). Reduced intestinal motility due to anticholinergic effects is a key mechanism (*5*). A systematic review showed that nine out of 11 studies reported a significant association between anticholinergic burden (ACB) and constipation (*6*). However, the majority of these studies were Western research, using non-Japanese tools such as the ACB Scale, Anticholinergic Risk Scale, and Drug Burden Index.

Released in May 2024, the Japanese Anticholinergic Risk Scale (JARS, 2nd edition) assigns a score of 0–3 to individual drugs, reflecting commonly used domestic medications (*7*). Nonetheless, the clinical utility of the JARS, particularly its associations with specific adverse outcomes such as constipation, requires validation in real-world settings.

Healthcare utilization databases enable large pharmacoepidemiologic evaluations (*8,9*). Despite being smaller than national databases, pharmacy chain–level datasets provide detailed longitudinal prescription data and integrate dispensing records across outlets (*10*). Utilizing such data, this study aimed to quantify the total JARS burden and examine its association with laxative prescription to explore the clinical utility of JARS in routine care.

2. Patients and Methods

2.1. Study design and population

This cross-sectional study used dispensing claims from community pharmacies operated by Qol Co., Ltd. (Tokyo, Japan). Eligible participants included outpatients aged ≥

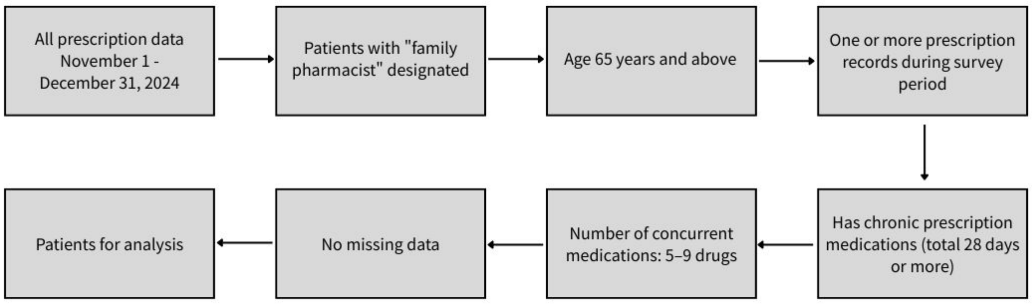

Figure 1. Patient selection flowchart. The inclusion criteria were as follows: outpatients aged ≥ 65 years who were registered with a family pharmacist, with at least one dispensing record between November 1 and December 31, 2024, and at least one chronic prescription (≥ 28 total days). The analytic cohort was restricted to patients receiving 5–9 concomitant chronic medications. Records with missing data were excluded.

65 years who were registered with a family pharmacist ("kakaritsuke pharmacist") between November 1 and December 31, 2024. Introduced in 2016, the family pharmacist system allows designated pharmacists to manage patients' medication information with their consent across institutions (*11,12*).

Chronic medication use was defined as prescriptions totaling ≥ 28 days within the two-month study window, which is consistent with previous studies and Japanese pharmacy claims research (*13,14*). The two-month observation window was selected because it highlights the consistent prescription patterns across various dispensing records while aligning with the definition of chronic use (≥ 28 days). The study period (November–December) was chosen because this pragmatic timeframe was close to implementation and avoided extreme seasonal temperatures.

To ensure internal consistency and sufficient exposure groups, the primary analysis was restricted to patients with 5–9 concomitant chronic medication prescriptions. This criterion aligns with the widely accepted polypharmacy definition (≥ 5 drugs) (*15*). Additionally, sensitivity under other thresholds requires future studies (*8,16*). Patients with ≥ 1 dispensing record and at least one chronic medication were included in the analysis, whereas those with missing data were excluded (Figure 1).

2.2. ACB assessment

For each patient, days of chronic medication use were aggregated using national reimbursement codes, while the total burden was estimated using the JARS scores (0–3). Total JARS burden was categorized as 0, 1, 2, 3, 4, or ≥ 5 points to enable detailed assessment of stepwise increase in medication burden. This categorization was guided by a recent pharmacovigilance study reporting a mean total anticholinergic load of 4.20 ± 3.09 in anticholinergic syndrome-related adverse events (*17*), suggesting potential clinical relevance at higher burden levels. Weekly formulations or topicals with systemic effects (*e.g.*, transdermal systems, corticosteroid topicals) were included in the assessment when used for chronic conditions.

Table 1. Classes of laxatives and representative generic drugs

Class	Generic names
Saline laxatives	Magnesium oxide, magnesium hydroxide
Stimulant laxatives	Sennosides (senna), sodium picosulfate, bisacodyl
Osmotic laxatives	Macrogol (polyethylene glycol, PEG) 4000, lactulose, sorbitol
Intestinal epithelial function modifiers (secretagogues)	Linaclotide, lubiprostone
IBAT inhibitor	Elobixibat
Kampo formula	Daiokanzoto
Agents for opioid-induced constipation	Naldemedine

Abbreviation: IBAT, ileal bile acid transporter.

2.3. Definition and classification of laxatives

The primary endpoint was chronic laxative use. A laxative was defined as *i*) a drug indicated for chronic constipation, *ii*) a stimulant laxative, or *iii*) a saline laxative prescribed for ≥ 28 days during the study window. Classes and representative generic names are listed in Table 1.

2.4. Covariates and medication counts

A set of covariates, including age, sex, and number of concomitant chronic medications (considering only drugs supplied for ≥ 28 days), were incorporated in the analysis. Weekly formulations or topicals with

systemic effects were included. Opioid use was initially considered a confounder; however, it was not included in the covariate adjustments because of sparse data (opioids were used in only 7 patients [0.07%]).

2.5. Statistical analysis

Patient characteristics were summarized descriptively. The association between JARS burden and laxative prescription was modeled using multivariable logistic regression, with JARS = 0 serving as the reference; adjustment was made for age, sex, and medication count. A secondary analysis with the same covariate adjustments was conducted using any drug rated 3 on the JARS as the exposure. Analyses were performed using the JMP software (SAS Institute Inc., Cary, NC, USA), with a two-sided $\alpha = 0.05$.

2.6. Ethical considerations

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki (2013 revision) and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Japan, 2021; revised 2023). Ethical approval was obtained from the Qol Institutional Review Board (approval no. QOL-091). Existing dispensing records were utilized using an opt-out consent approach *via* the facility's website, and data were anonymized prior to analysis.

Table 2. Baseline characteristics of the study population (*n* = 9,838)

Characteristic	Total
Age, years, mean ± SD	81.1 ± 7.3
65–74 years, *n* (%)	1,885 (19.1%)
75–84 years, *n* (%)	4,601 (46.8%)
≥ 85 years, *n* (%)	3,352 (34.1%)
Sex, *n* (%)	
Men	3,830 (38.9%)
Women	6,008 (61.1%)
Number of concomitant chronic medications, mean ± SD	6.6 ± 1.4
Medication count categories, *n* (%)	
5 drugs	2,596 (26.4%)
6 drugs	2,387 (24.3%)
7 drugs	2,007 (20.4%)
8 drugs	1,634 (16.6%)
9 drugs	1,214 (12.3%)
Total JARS score, *n* (%)	
0	3,878 (39.4%)
1	3,268 (33.2%)
2	1,447 (14.7%)
3	692 (7.0%)
4	305 (3.1%)
≥ 5	248 (2.5%)
Laxative prescription, *n* (%)	2,807 (28.5%)
Opioid use, *n* (%)	7 (0.07%)

Abbreviation: JARS, Japanese Anticholinergic Risk Scale.

3. Results

3.1. Patient characteristics

A total of 9,838 patients (mean age, 81.1 ± 7.3 years) were included in this study. Among the participants, men and women accounted for 38.9% and 61.1%, respectively. The mean number of chronic medications prescribed was 6.6 ± 1.4. Opioids were rarely used (*n* = 7, 0.07%) (Table 2).

3.2. Distribution of total JARS burden

Total JARS burden was categorized as 0 in 39.4% (*n* = 3,878) of the patients, 1 in 33.2% (*n* = 3,268), 2 in 14.7% (*n* = 1,447), 3 in 7.0% (*n* = 692), 4 in 3.1% (*n* = 305), and ≥ 5 in 2.5% (*n* = 248). With higher JARS scores, the proportion of women (JARS = 0: 61.2%, JARS = 1: 60.0%, JARS = 2: 61.1%, JARS = 3: 63.0%, JARS = 4: 68.2%, and JARS ≥ 5: 58.5%) and medication count (JARS = 0: 6.4 ± 1.3, JARS = 1: 6.6 ± 1.3, JARS = 2: 7.0 ± 1.4, JARS = 3: 7.1 ± 1.4, JARS = 4: 7.2 ± 1.4, and JARS ≥ 5: 7.2 ± 1.4) increased (Table 3).

3.3. Laxative prescription

Overall, 2,807 (28.5%) patients were treated with laxatives. Descriptions on laxative classes and usage patterns are presented in Table 4.

3.4. Association between the total JARS burden and laxative prescription

Crude laxative-prescription rates were 29.3% for JARS = 0, 26.5% for JARS = 1, 27.0% for JARS = 2, 30.5% for JARS = 3, 35.4% for JARS = 4, and 37.9% for JARS

Table 3. Patient characteristics by total JARS score category

Characteristic	0 point	1 point	2 points	3 points	4 points	≥ 5 points
n	3,878	3,268	1,447	692	305	248
Age, years, mean ± SD	81.8 ± 7.0	81.0 ± 7.3	81.1 ± 7.6	80.8 ± 7.5	80.2 ± 7.9	76.4 ± 7.9
Women, %	61.2	60.0	61.1	63.0	68.2	58.5
Number of concomitant chronic medications, mean ± SD	6.4 ± 1.3	6.6 ± 1.3	7.0 ± 1.4	7.1 ± 1.4	7.2 ± 1.4	7.2 ± 1.4
Laxative prescription, %	29.3	26.5	27.0	30.5	35.4	37.9

Abbreviation: JARS, Japanese Anticholinergic Risk Scale.

≥ 5. Multivariable logistic regression analysis (with 0 as the reference) indicated adjusted odds ratios (aORs) of 0.85 (95% confidence interval [CI]: 0.76–0.94, $p = 0.003$) for JARS = 1; 0.79 (95% CI: 0.69–0.91, $p = 0.001$) for JARS = 2; 0.94 (95% CI: 0.79–1.13, $p = 0.537$) for JARS = 3; 1.20 (95% CI: 0.93–1.55, $p = 0.153$) for JARS = 4; and 1.64 (95% CI: 1.24–2.16, $p < 0.001$) for JARS ≥ 5, revealing a stepwise increase with a significant positive association at the highest burden (Table 3, Figure 2).

3.5. Secondary analysis on drugs rated 3 on the JARS

Compared with the non-use of drugs rated 3 on the JARS, the use of such drugs was significantly linked with higher odds of laxative prescription (aOR: 1.71, 95% CI: 1.38–2.12, $p < 0.001$).

4. Discussion

This cross-sectional study assessed older outpatients to examine the association between the JARS and laxative prescriptions using community pharmacy claims. Our results revealed that total JARS burden ≥ 5 was significantly associated with laxative prescription, with the use of drugs rated 3 on the JARS showing an independent significant association. The laxative prescription rate revealed a stepwise increase across JARS categories, with rates of 29.3% for JARS = 0; 26.5% for JARS = 1; 27.0% for JARS = 2; 30.5% for JARS = 3; 35.4% for JARS = 4; and 37.9% for JARS = ≥ 5. The aOR for the ≥5 points group was 1.64 (95% CI: 1.24–2.16, $p < 0.001$), representing a clinically substantial increase. Notably, JARS = 1–2 groups showed significantly lower odds (aOR = 0.85 (95% CI: 0.76–0.94) and 0.79 (95% CI: 0.69–0.91), respectively) compared with the reference group, while the JARS = 3 group exhibited no significant difference (aOR = 0.94 , 95% CI: 0.79–1.13), and the JARS = 4 group demonstrated a trend toward increased odds that did not attain statistical significance (OR = 1.20, 95% CI: 0.93–1.55). This finding is consistent with the hypothesis that higher anticholinergic burden may be associated with constipation, with symptoms manifesting clinically primarily in the highest burden patients. These findings provide preliminary support for identifying patients more likely to be prescribed laxatives.

In the secondary analysis, the use of drugs rated 3 on the JARS showed high independent association with laxative prescription (aOR = 1.71, 95% CI: 1.38–2.12), suggesting that specific high-risk medications may be strongly associated with constipation beyond the cumulative burden score. This finding underscores the criticality of individual drug properties, apart from the total score summation. Notably, antimuscarinic agents prescribed for overactive bladder have consistently been reported to cause constipation as a major side-effect (*18,19*). In addition, drugs possessing strong anticholinergic properties are recognized for carrying elevated constipation risk.

The lower aORs for JARS = 1–2 may reflect residual

Table 4. Use of laxatives by class among patients receiving any laxative (*n* = 2,807)

Class	Patients, *n*	Share among laxative users, %
Saline laxatives	1,933	68.9
Stimulant laxatives	908	32.3
Osmotic laxatives	120	4.3
Intestinal epithelial function modifiers (secretagogues)	291	10.4
IBAT inhibitor	123	4.4
Kampo formula	13	0.5
Agents for opioid-induced constipation	7	0.2
Total laxative users	2,807 (28.5% of cohort)	—
Monotherapy	2,299	81.9
Combination therapy	508	18.1

Abbreviation: IBAT, ileal bile acid transporter.

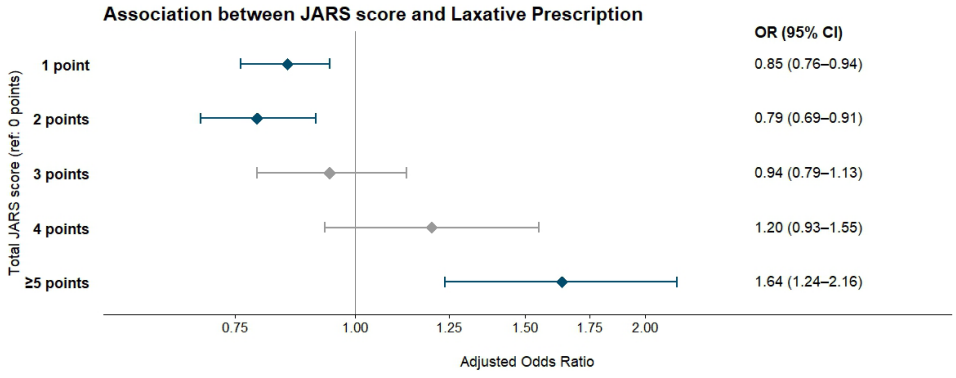

Figure 2. Association between the total JARS score and laxative prescription (forest plot). Adjustments were made for age, sex, and number of concomitant chronic medications. Squares represent point estimates, whereas horizontal bars indicate 95% confidence intervals. The dashed vertical line represents an odds ratio of 1.0 (no association). Reference category: JARS = 0. *Abbreviation*: JARS, Japanese Anticholinergic Risk Scale.

confounding from non-anticholinergic constipating drugs (*e.g.*, iron, nonsteroidal anti-inflammatory drugs, calcium channel blockers, opioids) and possible threshold effects where mild anticholinergic exposure does not induce clinically significant constipation. For instance, some calcium channel blockers and opioids are assigned 1–2 points on the JARS, implying these drugs may be dispersed across the 0–2 point categories. This broad distribution potentially contributes to confounding. Therefore, future analyses should focus on adjusting for both anticholinergic effects and constipation-inducing properties of medications, and model the JARS score as a continuous variable to evaluate nonlinear associations.

The higher proportion of females with increasing JARS burden likely reflects sex-specific disease patterns (*e.g.*, overactive bladder, depression), suggesting a higher occurrence of constipation in women (*20–23*). The prevalence of overactive bladder has been reported as 21.9% in women (*20*), while systematic reviews have revealed this rate to be approximately twice as high in women compared with men (*22*). However, given the limited information on indications and symptom severity in this study, it is difficult to fully disentangle the primary contributing factors.

Slightly younger age in higher-burden groups may indicate cautious avoidance of strong anticholinergic medications by the oldest patients. Detailed information on laxative classes and usage patterns is presented in Table 4, with saline and stimulant laxatives being the predominant treatment types, in accordance with Japanese practice (*24*).

This study has several limitations that warrant consideration. First, the cross-sectional design precludes the establishment of temporal relationships between anticholinergic exposure and laxative prescription; therefore, causal inferences cannot be drawn. Protopathic bias may also be present, as laxatives could have been prescribed before or concurrently with anticholinergic medications, rather than as a consequence of anticholinergic exposure. Second, dispensing claims lack clinical details, leaving residual confounding unaddressed. Potential confounders not captured in our data include dietary factors (*e.g.*, fiber intake, fluid consumption), physical activity, the severity of underlying diseases, and the use of non-anticholinergic constipating medications (*e.g.*, iron supplements, calcium channel blockers, non-steroidal anti-inflammatory drugs). Although we attempted to account for opioid use, the sparse data ($n = 7$) precluded meaningful adjustment. Third, laxative prescriptions were used as a surrogate marker for constipation; however, this may not fully reflect the actual occurrence or severity of constipation. Patients may have managed symptoms with over-the-counter laxatives or dietary modifications not captured in prescription claims. In addition, laxatives may have been prescribed prophylactically or for indications not directly reflecting constipation severity, which may have introduced outcome misclassification. Fourth, the restriction to patients receiving 5–9 concomitant chronic medications limits the generalizability of our findings to broader populations.

Despite these limitations, this study represents the first real-world evaluation linking the JARS to constipation-related prescriptions in Japan. The results suggest that the JARS may serve as a practical strategy for ACB assessment. The study also underscores the need for proactive constipation-risk management in patients with high JARS burden. Future research should investigate other anticholinergic outcomes (*e.g.*, cognitive impairment, falls, urinary retention) and drug-specific risk profiles to guide safer alternatives and inform better disease mitigation strategies.

In conclusion, higher ACB (total JARS burden ≥ 5) and the use of drugs rated 3 on the JARS were significantly associated with laxative prescription in older adults. These findings provide preliminary support for the potential clinical utility of the JARS. Future longitudinal studies are needed to confirm these associations and establish temporal relationships.

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Retrospective observational analysis of prasugrel dosage after percutaneous coronary intervention using the Clinical Deep Data Accumulation System database

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Abstract: Prasugrel reduces the recurrence of atherosclerotic cardiovascular disease and restenosis after percutaneous coronary intervention (PCI). However, its actual dosage in Japan has not been well studied. This study aimed to compare different prasugrel doses after PCI using retrospective data from the Clinical Deep Data Accumulation System (CLIDAS) database. A retrospective observational study was conducted using the CLIDAS-PCI database with a 2-year follow-up after PCI. There were 2,869 and 52 patients in the 3.75- and 2.5 mg groups, respectively. The 2.5 mg group was comprised of significantly more female, older, shorter, and lower-body-weight patients and included more patients with a history of coronary artery bypass grafting, stroke, peripheral arterial disease, or active malignancy than the 3.75 mg group. Concomitant medications included antiplatelets, anticoagulants, and statins. Laboratory data showed substantially lower hemoglobin and platelet counts in the 2.5 mg group. Most patients weighed < 50 kg; however, fewer had an estimated glomerular filtration rate < 30 mL/min/1.73 m². Major adverse cardio- and cerebrovascular events were similar between groups. The 2.5 mg group had more non-fatal strokes and major bleeding associated with antithrombotic therapy. In Japan, prasugrel 2.5 mg should be considered to reduce major bleeding in patients with low body weight, older adults, women, those receiving concomitant antithrombotic therapy, and those with low platelet counts.

***Keywords*:** prasugrel, major adverse cardiovascular and cerebrovascular events (MACCE), Clinical Deep Data Accumulation System (CLIDAS), percutaneous coronary intervention (PCI)

1. Introduction

Prasugrel is a third-generation thienopyridine antiplatelet drug that rapidly and potently inhibits platelet aggregation. Unlike clopidogrel, its action is not affected by CYP2C19 genetic polymorphisms. In the TRITON-TIMI 38 study of percutaneous coronary intervention (PCI) of acute coronary syndrome (ACS), prasugrel (60 mg loading dose [LD]/10 mg maintenance dose [MD]) resulted in considerably fewer ischemic cardiovascular events than clopidogrel but was associated with increased major bleeding not related to coronary artery bypass grafting (CABG). The risk of bleeding was particularly high in patients aged > 75 years, those with body weight < 60 kg, and those with a history of stroke or transient ischemic attack (TIA) (*1*). The PRASIFIT-ACS study of emergent PCI in ACS (*2*) and the PRASIFIT-Elective study of scheduled PCI in patients with stable angina and old myocardial infarction (chronic coronary syndrome [CCS]) (*3*) showed that 3.75 mg of prasugrel was associated with significantly fewer ischemic cardiovascular accidents than the standard dose of clopidogrel, with similar bleeding risk. Prasugrel (20 mg LD/3.75 mg MD) has therefore been approved and widely used in Japan. According to the drug information, there were no differences in the pharmacokinetics of active metabolites in patients with moderate renal dysfunction (creatinine clearance 30–50 mL/min/1.73 m^2), moderate hepatic dysfunction (Child–Pugh class B), or in older patients (≥ 75 years) compared to healthy or non-older individuals. Antiplatelet therapy is especially important for patients at high bleeding risk (*4*). Since May 2014, a 2.5 mg MD of prasugrel has been available in Japan. The safety and efficacy of prasugrel (2.5 mg) in older and/or low-body-weight Japanese patients with ischemic stroke have been reported (*5*). A Japanese Phase II study in patients ≥ 75 years and/or ≤ 50 kg undergoing elective PCI demonstrated that prasugrel 20 mg LD/2.5 mg MD inhibits platelet function in a manner comparable to clopidogrel (*6*). The real use of prasugrel 2.5mg MD after PCI has not been reported. Therefore, in this study, we conducted a retrospective observational study using the Clinical Deep Data Accumulation System (CLIDAS) database, which follows post-PCI patients, to examine prasugrel use, selection background, cardiovascular events, and major bleeding in real-world clinical practice in Japan.

2. Patients and Methods

2.1. CLIDAS

Seven hospitals (six university hospitals and the National Cerebral and Cardiovascular Center Hospital in Japan) participated in the CLIDAS project. Standardized Structured Medical Information eXchange version 2 (SS-MIX2) standard storage was used to collect essential patient information, prescriptions, and laboratory data from electronic medical records, while SS-MIX2 extended storage was used to capture physiological test results, cardiac catheterization reports, and cardiac catheter intervention reports (*7*).

CLIDAS was developed as part of the Japan Ischemic Heart Disease Multimodal Prospective Data Acquisition for Precision Treatment Project, launched in 2015, which aimed to establish a hospital information system (HIS)-based procedure for electronically capturing medical records and other clinical data in standardized formats for clinical studies (*8*). Data from the HIS, picture archiving and communication system, and physiology server were linked to a multipurpose clinical data repository system (MCDRS) through the SS-MIX2 standard and extended storage. After anonymization, each facility's output data were sent through the MCDRS server to the CLIDAS server. Data managers and researchers at each facility collected patients' background information and follow-up data. Finally, the data stored on the CLIDAS server were analyzed (*9-13*).

2.2. Study design and clinical outcomes

This retrospective multicenter observational study included patients with coronary artery disease who underwent PCI at seven hospitals between May 2014 and December 2023 (*14*). Patients aged < 20 years, those without a prasugrel prescription within 14 days after PCI, and those with no event data after PCI were excluded. The final study population was divided into two groups based on the prasugrel dose. This study was approved by the Institutional Review Board for Clinical Research of the National Center for Global Health and Medicine (NCGM-S-004832-00) and conducted according to the ethical principles of the Declaration of Helsinki. The retrospective design waived the requirement for written informed consent.

The primary outcome was the incidence of major adverse cardiac and cerebrovascular events (MACCE) during the 2-year follow-up, defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary artery revascularization. Secondary outcomes included individual MACCE components and major bleeding. Major bleeding was defined as the need for transfusion of > 2 units of blood or a fall in hemoglobin level of ≥ 2.0 g/dL. Prasugrel dose was also considered a secondary outcome to evaluate the association between patient characteristics and dose selection.

2.3. Definitions

All baseline laboratory data were defined as the most recent values obtained within 14 days before

the index PCI. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or medical treatment for hypertension at the index PCI. Diabetes was defined as glycated hemoglobin ≥ 6.5%, casual blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, or medical treatment for diabetes at the index PCI. Dyslipidemia was defined as medical treatment for dyslipidemia at the index PCI or a recorded diagnosis of dyslipidemia in the electronic medical records. Current and past smokers were included in the smoking category. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine (Cr) concentration, age, weight, and sex using the following formula (*15*):

$$\mathrm{eGFR(ml/min/1.73m^2)} = \begin{cases} 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{age}^{-0.287} \text{ (in men)} \\ 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{age}^{-0.287} \times 0.739 \text{ (in women)} \end{cases}$$

Medication status was assessed by counting the number of prescriptions within 14 days prior to the index PCI. Each patient's prasugrel dose was determined as the dose administered for the greatest cumulative duration between the index PCI and the earliest occurrence of any event of interest.

2.4. Statistical analysis

Continuous variables are summarized as means ± standard deviations, and categorical variables as frequencies and percentages. Differences between dose groups were examined using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables, including the number of events for primary and secondary outcomes.

To explore factors associated with dose selection, logistic regression models were fitted with baseline characteristics as explanatory variables. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and *p*-values are reported.

For analyses of MACCE and major bleeding events, survival curves were estimated using the Kaplan–Meier method, and comparisons between dose groups were performed using log-rank tests. Cox proportional hazards models were used to evaluate relative risks between dose groups, providing hazard ratios (HRs) with 95% CIs and *p*-values. Cox models included dose groups and clinically important confounders as covariates.

Missing data were not imputed, and all analyses were conducted using a complete case approach. Statistical significance was defined as a two-sided p-value < 0.05. No adjustments for multiple testing were made due to the exploratory nature of the analyses. All statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

The CLIDAS database included 8,188 consecutive patients who underwent PCI between May 2014 and December 2023 (Figure 1). Patients aged < 20 years (n = 2), those without a prasugrel prescription within 14 days after PCI (n = 4,830), and those without event data after PCI (n = 50) were excluded. Of the remaining patients prescribed prasugrel (n = 3,306), those with an unconfirmed prasugrel dose from the time of PCI to the

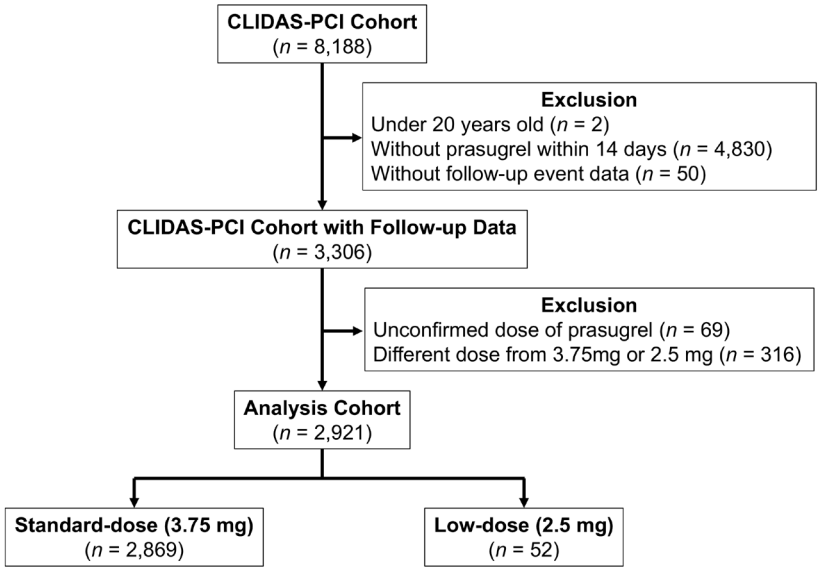

Figure 1. Flowchart of patient enrollment. Among the 8,188 patients in the CLIDAS-PCI cohort, 2,921 were included in this study. The 3.75 and 2.5 mg groups had 2,869 and 52 patients, respectively. *Abbreviations*: PCI, percutaneous coronary intervention; CLIDAS, Clinical Deep Data Accumulation System.

event (n = 69) or with doses different from 3.75 or 2.5 mg (n = 316) were excluded. The final study population included 2,921 patients, analyzed as the 3.75 (n = 2,869) and 2.5 mg groups (n = 52).

3.2. Baseline characteristics

Baseline characteristics of the two groups are presented in Table 1. The 2.5 mg group had a higher proportion of women (44.2% *vs.* 19.1%, $p < 0.001$), older age at PCI (78.3 ± 8.2 *vs.* 67.8 ± 11.3 years, $p < 0.001$), shorter height (157.6 ± 8.7 cm *vs.* 162.9 ± 9.0 cm, $p < 0.001$), lower weight (55.4 ± 11.0 kg *vs.* 65.0 ± 13.3 kg, $p < 0.001$) and lower body mass index (BMI) (22.1 ± 3.1 *vs.* 24.4 ± 3.9, $p < 0.001$) than the 3.75 mg group. Compared to the 3.75 mg group, the 2.5 mg group had fewer smokers (46.2% *vs.* 63.6%, $p = 0.008$), and more patients with a medical history of CABG surgery (9.6% *vs.* 3.1%, $p = 0.024$), stroke (13.5% *vs.* 6.0%, $p = 0.039$), peripheral artery disease (9.6% *vs.* 3.3%, $p = 0.036$), and active malignancy (19.2% *vs.* 10.2%, $p = 0.006$). Patients in the 2.5 mg group had higher rates of antiplatelet therapy (84.6% *vs.* 60.1%, $p < 0.001$), anticoagulants (26.9% *vs.* 3.9%, $p < 0.001$), and statins (30.8% *vs.* 19.1%, $p = 0.049$) than those in the 3.75 mg group. Laboratory data showed lower hemoglobin

Table 1. Baseline characteristics and cardiovascular events in the 3.75 and 2.5 mg groups

Variables	Total (n = 2,921)	3.75 mg (n = 2,869)	2.5 mg (n = 52)	p-value
Characteristics				
Female	571 (19.5%)	548 (19.1%)	23 (44.2%)	< 0.001
Age, years	68.0 ± 11.3	67.8 ± 11.3	78.3 ± 8.2	< 0.001
Height, cm	162.8 ± 9.0	162.9 ± 9.0	157.6 ± 8.7	< 0.001
Weight, kg	64.8 ± 13.3	65.0 ± 13.3	55.4 ± 11.0	< 0.001
BMI, kg/m^2	24.3 ± 3.9	24.4 ± 3.9	22.1 ± 3.1	< 0.001
Smoking	1,849 (63.3%)	1,825 (63.6%)	24 (46.2%)	0.008
Weight ≤ 50 kg	339 (11.6%)	320 (11.2%)	19 (36.5%)	< 0.001
Past medical history				
PCI	350 (12.0%)	341 (11.9%)	9 (17.3%)	0.278
CABG	93 (3.2%)	88 (3.1%)	5 (9.6%)	0.024
Myocaridal infarction	445 (15.2%)	439 (15.3%)	6 (11.5%)	0.562
Heart failure	135 (4.6%)	130 (4.5%)	5 (9.6%)	0.091
Stroke	180 (6.2%)	173 (6.0%)	7 (13.5%)	0.039
Complications				
Diabetes mellitus	1,184 (40.5%)	1,162 (40.5%)	22 (42.3%)	0.887
Dyslipidemia	2,268 (77.6%)	2,232 (77.8%)	36 (69.2%)	0.126
Hypertension	2,299 (78.7%)	2,257 (78.7%)	42 (80.8%)	0.865
Peripheral arterial disease	99 (3.4%)	94 (3.3%)	5 (9.6%)	0.036
Atrial fibrillation	86 (2.9%)	83 (2.9%)	3 (5.8%)	0.198
Hemodialysis	133 (4.6%)	132 (4.6%)	1 (1.9%)	0.731
Active maligancy	304 (10.4%)	294 (10.2%)	10 (19.2%)	0.006
Medications				
Antiplatelet	1,767 (60.5%)	1,723 (60.1%)	44 (84.6%)	< 0.001
Anticoagulant	126 (4.3%)	112 (3.9%)	14 (26.9%)	< 0.001
Statin	565 (19.3%)	549 (19.1%)	16 (30.8%)	0.049
Antihypertensive drug	969 (33.2%)	958 (33.4%)	11 (21.2%)	0.074
Laboratory variables				
eGFR, mL/min/1.73 m^2	63.7 ± 24.8	63.8 ± 24.9	62.6 ± 18.5	0.655
Hemoglobin, g/dL	13.0 ± 1.9	13.0 ± 1.9	11.9 ± 1.7	< 0.001
Platelet, 10^3/μL	111.5 ± 103.6	112.9 ± 103.8	35.8 ± 54.5	< 0.001
Creatinin, mg/dL	1.3 ± 1.7	1.3 ± 1.8	1.0 ± 0.8	0.002
eGFR ≤ 30 mL/min/1.73 m^2	244 (8.4%)	242 (8.4%)	2 (3.8%)	0.006
PCI				
ACS	1,438 (49.2%)	1,419 (49.5%)	19 (36.5%)	0.070
CCS	1,482 (50.7%)	1,449 (50.5%)	33 (63.5%)	
Cardiovascular events				
MACCE	865 (29.6%)	853 (29.7%)	12 (23.1%)	0.359
Non-fatal myocardial infarction	65 (2.2%)	65 (2.3%)	0 (0.0%)	0.630
Non-fatal stroke	36 (1.2%)	33 (1.2%)	3 (5.8%)	0.025
Cardiovascular death	57 (2.0%)	57 (2.0%)	0 (0.0%)	0.625
Coronary revasculization	727 (24.9%)	718 (25.0%)	9 (17.3%)	0.257
Major bleeding	45 (1.5%)	41 (1.4%)	4 (7.7%)	0.008

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

(11.9 ± 1.7 g/dL *vs.* 13.0 ± 1.9 g/dL, $p < 0.001$), platelet count (35.8 ± 54.5 × 10^3/μL *vs.* 112.9 ± 103.8 × 10^3/μL, $p < 0.001$), and creatinine (1.0 ± 0.8 mg/dL *vs.* 1.3 ± 1.8 mg/dL, $p = 0.002$) in the 2.5 mg group. More patients in the 2.5 mg group weighed < 50 kg (36.5% *vs.* 11.2%, $p < 0.001$), and fewer had an eGFR ≤ 30 ml/min/1.73 m^2 (3.8% *vs.* 8.4%, $p = 0.006$) than the 3.75 mg group.

3.3. MACCE and major bleeding

No significant difference was observed between the two groups in the incidence of MACCE (23.1% *vs.* 29.7%, $p = 0.359$) or coronary revascularization procedures (17.3% *vs.* 25.0%, $p = 0.257$). The 2.5 mg group had higher rates of nonfatal stroke (5.8% *vs.* 1.2%, $p = 0.025$) and major bleeding (7.7% *vs.* 1.4%, $p = 0.008$) than the 3.75 mg group (Table 1).

Kaplan–Meier curves for MACCE and major bleeding are shown in Figures 2A and B. In the 2.5 mg group, MACCE showed a non-significant downward trend at 1 year, whereas major bleeding occurred significantly more frequently than in the 3.75 mg group.

3.4. Sub-analysis by ACS or CCS

In the ACS group (n = 1,438), only 0.97% (n = 19) received prasugrel (2.5 mg), the majority of whom were women (n = 14, 73.7%) (Table 2). History of stroke (21.1% *vs.* 4.7%, $p = 0.012$), anticoagulant use (31.6% *vs.* 2.4%, $p < 0.001$), and major bleeding (10.5% *vs.* 1.5%, $p = 0.035$) were more common, while hemoglobin levels were lower (11.7 ± 1.9 g/dL *vs.* 13.3 ± 1.9 g/dL, $p = 0.002$) in the 2.5 mg group. MACCE tended to be lower in the 2.5 mg group (10.5% *vs.* 30.5%, $p = 0.077$).

In scheduled PCI (CCS), the 2.5 mg group had more patients with active malignancy (24.2% *vs.* 13.3%, $p = 0.024$), higher anticoagulant use (21.2% *vs.* 4.9%, $p = 0.001$), and lower platelet counts (21.3 ± 6.9 x 10^3/μL *vs.* 126.5 ± 100.2 × 10^3/μL, $p < 0.001$) than the 3.75 mg group. The 2.5 mg group showed a lower tendency for MACCE, while the incidence of major bleeding was similar between groups (Table 2).

3.5. Sub-analysis by body weight

The package insert for prasugrel states that a 2.5 mg dose may be considered for patients weighing ≤ 50 kg. Therefore, patients were divided into two groups: Weight ≤ 50 kg and Weight > 50 kg (Table 3). In the Weight ≤ 50 kg group (n = 339), only 5.6% (n = 19) were prescribed prasugrel (2.5 mg). Compared to the 3.75 mg group (n = 320), patients receiving 2.5 mg prasugrel had a higher proportion of women (89.5% *vs.* 65.6%, $p = 0.042$), older age at PCI (80.0 ± 7.2 years *vs.* 75.1 ± 9.8 years, $p = 0.01$), higher prevalence of active malignancy (26.3% *vs.* 13.1%, $p = 0.007$), more frequent use of antiplatelet agents (89.5% *vs.* 59.4%, $p = 0.008$) and anticoagulants (21.1% *vs.* 5.3%, $p = 0.023$), lower platelet counts (55.5 ± 77.2 x 10^3/μL *vs.* 119.5 ± 108.9 × 10^3/μL, $p < 0.001$), and a higher proportion experiencing major bleeding (15.8% *vs.* 2.2%, $p = 0.014$). The MACCE rate was not significantly different (15.8% *vs.* 23.1%, $p = 0.582$).

In the Weight > 50 kg group (n = 2,348), the 2.5 mg group (n = 33) had higher age (77.4 ± 8.7 years *vs.* 66.6 ± 11.1 years, $p < 0.001$), shorter height (161.7 ± 6.9 cm *vs.* 164.6 ± 7.9 cm, $p = 0.025$), lower BMI (23.8 ± 2.2 *vs.* 25.0 ± 3.6, $p = 0.004$), and higher prevalence of prior CABG (15.2% *vs.* 3.1%, $p = 0.004$) and prior stroke (15.2% *vs.* 5.4%, $p = 0.033$) than the 3.75 mg group (n = 2,315). The 2.5 mg group also had higher

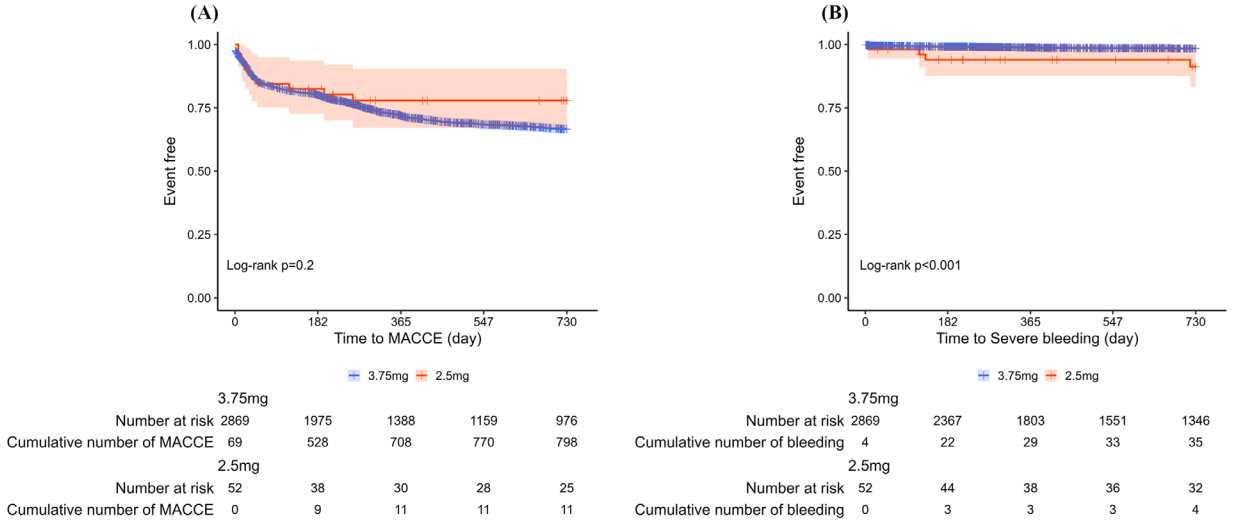

Figure 2. Kaplan–Meier curves of (A) MACCE and (B) major bleeding. *Abbreviations*: MACCE, major adverse cardiovascular and cerebrovascular events (MACCE).

Table 2. Sub-analysis by ACS or CCS

Variables	ACS (n = 1,438)			CCS (n = 1,482)		
	3.75 mg (n = 1,419)	2.5 mg (n = 19)	p-value	3.75 mg (n = 1,449)	2.5 mg (n = 33)	p-value
Characteristics						
Female	277 (19.5%)	14 (73.7%)	< 0.001	271 (18.7%)	9 (27.3%)	0.381
Age, years	66.7 ± 12.0	77.5 ± 6.7	< 0.001	68.9 ± 10.5	78.8 ± 9.1	< 0.001
Height, cm	163.3 ± 8.8	153.3 ± 8.1	< 0.001	162.6 ± 9.2	160.2 ± 8.2	0.105
Weight, kg	65.4 ± 13.4	49.5 ± 10.1	< 0.001	64.5 ± 13.1	58.8 ± 10.1	0.003
BMI, kg/m^2	24.4 ± 4.0	21.0 ± 3.6	< 0.001	24.3 ± 3.9	22.8 ± 2.7	0.003
Weight ≤ 50 kg	153 (10.8%)	10 (52.6%)	< 0.001	167 (11.5%)	9 (27.3%)	0.031
Smoking	940 (66.2%)	9 (47.4%)	0.083	885 (61.1%)	15 (45.5%)	0.069
Past medical history						
PCI	124 (8.7%)	4 (21.1%)	0.083	216 (14.9%)	5 (15.2%)	> 0.999
CABG	30 (2.1%)	2 (10.5%)	0.065	58 (4.0%)	3 (9.1%)	0.153
Myocaridal infarction	206 (14.5%)	2 (10.5%)	> 0.999	232 (16.0%)	4 (12.1%)	0.810
Heart failure	36 (2.5%)	2 (10.5%)	0.088	94 (6.5%)	3 (9.1%)	0.475
Stroke	66 (4.7%)	4 (21.1%)	0.012	107 (7.4%)	3 (9.1%)	0.732
Complications						
Diabetes mellitus	511 (36.0%)	7 (36.8%)	> 0.999	650 (44.9%)	15 (45.5%)	> 0.999
Dyslipidemia	1,141 (80.4%)	11 (57.9%)	0.018	1,090 (75.2%)	25 (75.8%)	> 0.999
Hypertension	1,146 (80.8%)	15 (78.9%)	0.767	1,110 (76.6%)	27 (81.8%)	0.676
Peripheral arterial disease	29 (2.0%)	1 (5.3%)	0.343	65 (4.5%)	4 (12.1%)	0.077
Atrial fibrillation	27 (1.9%)	0 (0.0%)	> 0.999	56 (3.9%)	3 (9.1%)	0.142
Hemodialysis	45 (3.2%)	1 (5.3%)	0.465	87 (6.0%)	0 (0.0%)	0.257
Active maligancy	101 (7.1%)	2 (10.5%)	0.146	193 (13.3%)	8 (24.2%)	0.024
Medications						
Antiplatelet	651(45.9%)	11 (57.9%)	0.357	787 (54.3%)	23 (69.7%)	0.110
Anticoagulants	34 (2.4%)	6 (31.6%)	< 0.001	71 (4.9%)	7 (21.2%)	0.001
Statin	226 (15.9%)	4 (21.1%)	0.528	262 (18.1%)	8 (24.2%)	0.362
Antihypertensive drug	368 (25.9%)	3 (15.8%)	0.432	437 (30.2%)	4 (12.1%)	0.032
Laboratory variables						
eGFR, mL/min/1.73 m^2	66.1 ± 25.7	59.1 ± 21.8	0.182	61.4 ± 23.8	64.6 ± 16.3	0.277
Hemoglobin, g/dL	13.3 ± 1.9	11.7 ± 1.9	0.002	13.0 ± 1.8	12.4 ± 1.6	0.041
Platelet, 10^3/μL	100.4 ± 107.0	63.1 ± 88.8	0.086	126.5 ± 100.2	21.3 ± 6.9	< 0.001
Creatinin, mg/dL	1.2 ± 1.5	1.1 ± 1.3	0.661	1.4 ± 1.9	0.9 ± 0.3	< 0.001
eGFR ≤ 30 mL/min/1.73 m^2	117 (8.2%)	1 (5.3%)	> 0.999	125 (8.6%)	1 (3.0%)	0.363
Cardiovascular events						
MACCE	433 (30.5%)	2 (10.5%)	0.077	419 (28.9%)	10 (30.3%)	0.848
Non-fatal myocardial infarction	59 (4.2%)	0 (0.0%)	> 0.999	6 (0.4%)	0 (0.0%)	> 0.999
Non-fatal stroke	20 (1.4%)	1 (5.3%)	0.245	13 (0.9%)	2 (6.1%)	0.042
Cardiovascular death	35 (2.5%)	0 (0.0%)	> 0.999	22 (1.5%)	0 (0.0%)	> 0.999
Coronary revasculization	334 (23.5%)	1 (5.3%)	0.096	383 (26.4%)	8 (24.2%)	> 0.999
Major bleeding	21 (1.5%)	2 (10.5%)	0.035	20 (1.4%)	2 (6.1%)	0.084

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

rates of antiplatelet therapy (81.8% *vs.* 58.7%, p = 0.007), anticoagulant therapy (30.3% *vs.* 3.3%, p < 0.001), and statin use (33.3% *vs.* 17.8%, p = 0.036), but the incidence of MACCE was similar between the groups (27.3% *vs.* 31.4%, p = 0.708).

3.6. Sub-analysis by Renal Function (eGFR)

Although renal function is not known to affect prasugrel metabolism, patients were classified based on eGFR into a severe renal impairment group (eGFR ≤ 30 ml/min/1.73 m^2, n = 244) and an eGFR > 30 ml/min/1.73 m^2 group (n = 2,329). In the eGFR ≤ 30 ml/min/1.73 m^2 group, only two patients received 2.5 mg prasugrel; therefore, statistical analysis was not possible (Table 4). In the eGFR > 30 ml/min/1.73 m^2 group, results were consistent with the overall patient analysis: nonfatal stroke (5.0% *vs.* 1.0%, p = 0.018) and major bleeding (6.0% *vs.* 1.3%, p = 0.033) were higher in the 2.5 mg group than in the 3.75 mg group.

3.7. Sub-analysis by sex

Sex is an important factor for cardiovascular disease; therefore, a sex-specific sub-analysis was performed (Table 5). In the male group (n = 2,180), the 2.5 mg group (n = 29) had higher age (76.3 ± 8.6 years *vs.* 66.6 ± 11.2 years, p < 0.001), shorter height (163.7 ± 4.6 cm *vs.*

Table 3. Sub-analysis by body weight

Variables	Weight > 50 kg (n = 2,348)			Weight ≤ 50 kg (n = 339)		
	3.75 mg (n = 2,315)	2.5 mg (n = 33)	p-value	3.75 mg (n = 320)	2.5 mg (n = 19)	p-value
Characteristics						
Female	326 (14.1%)	6 (18.2%)	0.454	210 (65.6%)	17 (89.5%)	0.042
Age, years	66.6 ± 11.1	77.4 ± 8.7	< 0.001	75.1 ± 9.8	80.0 ± 7.2	0.010
Height, cm	164.6 ± 7.9	161.7 ± 6.9	0.025	151.5 ± 7.7	150.5 ± 7.0	0.574
BMI, kg/m^2	25.0 ± 3.6	23.8 ± 2.2	0.004	19.6 ± 2.3	19.2 ± 2.4	0.571
Smoking	1,568 (67.7%)	18 (54.5%)	0.089	113 (35.3%)	6 (31.6%)	0.809
Past medical history						
PCI	272 (11.7%)	8 (24.2%)	0.051	38 (11.9%)	1 (5.3%)	0.710
CABG	72 (3.1%)	5 (15.2%)	0.004	10 (3.1%)	0 (0.0%)	> 0.999
Myocaridal infarction	329 (14.2%)	5 (15.2%)	0.804	53 (16.6%)	1 (5.3%)	0.331
Heart failure	98 (4.2%)	3 (9.1%)	0.169	24 (7.5%)	2 (10.5%)	0.650
Stroke	125 (5.4%)	5 (15.2%)	0.033	21 (6.6%)	2 (10.5%)	0.381
Complications						
Diabetes mellitus	960 (41.5%)	16 (48.5%)	0.481	115 (35.9%)	6 (31.6%)	0.808
Dyslipidemia	1,838 (79.4%)	26 (78.8%)	0.828	229 (71.6%)	10 (52.6%)	0.072
Hypertension	1,829 (79.0%)	27 (81.8%)	> 0.999	2,490 (77.8%)	15 (78.9%)	> 0.999
Peripheral arterial disease	66 (2.9%)	3 (9.1%)	0.082	16 (5.0%)	2 (10.5%)	0.283
Atrial fibrillation	71 (3.1%)	2 (6.1%)	0.276	6 (1.9%)	1 (5.3%)	0.337
Hemodialysis	94 (4.1%)	0 (0.0%)	0.642	23 (7.2%)	1 (5.3%)	> 0.999
Active maligancy	220 (9.5%)	5 (15.2%)	0.245	42 (13.1%)	5 (26.3%)	0.007
Medications						
Antiplatelet	1,359 (58.7%)	27 (81.8%)	0.007	190 (59.4%)	17 (89.5%)	0.008
Anticoagulant	77 (3.3%)	10 (30.3%)	< 0.001	17 (5.3%)	4 (21.1%)	0.023
Statin	413 (17.8%)	11 (33.3%)	0.036	50 (15.6%)	5 (26.3%)	0.209
Antihypertensive drug	765 (33.0%)	6 (18.2%)	0.092	93 (29.1%)	5 (26.3%)	> 0.999
Laboratory variables						
eGFR, mL/min/1.73 m^2	64.4 ± 24.7	61.1 ± 15.0	0.221	58.6 ± 25.8	65.2 ± 23.7	0.261
Hemoglobin, g/dL	13.3 ± 1.8	12.4 ± 1.7	0.006	11.5 ± 1.6	11.2 ± 1.3	0.337
Platelet, 10^3/μL	108.5 ± 102.6	24.4 ± 31.8	< 0.001	119.5 ± 108.9	55.5 ± 77.2	0.002
Creatinin, mg/dL	1.3 ± 1.7	0.9 ± 0.3	< 0.001	1.3 ± 1.6	1.0 ± 1.3	0.336
eGFR ≤ 30 mL/min/1.73 m^2	195 (8.4%)	1 (3.0%)	0.327	44 (13.8%)	1 (5.3%)	0.581
PCI						
ACS	1,175 (50.8%)	9 (27.3%)	0.008	153 (47.8%)	10 (52.6%)	0.814
CCS	1,139 (49.2%)	24 (72.7%)		167 (52.2%)	9 (47.4%)	
Cardiovascular events						
MACCE	727 (31.4%)	9 (27.3%)	0.708	74 (23.1%)	3 (15.8%)	0.582
Non-fatal myocardial infarction	54 (2.3%)	0 (0.0%)	> 0.999	4 (1.3%)	0 (0.0%)	> 0.999
Non-fatal stroke	26 (1.1%)	2 (6.1%)	0.058	5 (1.6%)	1 (5.3%)	0.294
Cardiovascular death	42 (1.8%)	0 (0.0%)	> 0.999	11 (3.4%)	0 (0.0%)	> 0.999
Coronary revasculization	623 (26.9%)	7 (21.2%)	0.556	55 (17.2%)	2 (10.5%)	0.751
Major bleeding	31 (1.3%)	1 (3.0%)	0.366	7 (2.2%)	3 (15.8%)	0.014

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

166.0 ± 6.7 cm, $p = 0.011$), lower body weight (62.7 ± 7.4 kg *vs.* 67.7 ± 12.9 kg, $p = 0.001$), and lower BMI (23.4 ± 2.6 *vs.* 24.5 ± 4.0, $p = 0.032$) than the 3.75 mg group (n = 2,151). However, the proportion of patients weighing ≤ 50 kg was similar in both groups (6.9% *vs.* 5.2%, $p = 0.826$). The 2.5 mg group had a higher prevalence of peripheral arterial disease (13.8% *vs.* 3.0%, $p = 0.014$), antiplatelet therapy (82.8% *vs.* 59.6%, $p = 0.012$), and anticoagulant therapy (34.5% *vs.* 3.4%, $p < 0.001$). Laboratory data showed lower hemoglobin (12.7 ± 1.5 g/dL *vs.* 13.4 ± 1.8 g/dL, $p = 0.021$), platelet count (19.9 ± 6.2 × 10^3/μL *vs.* 104.6 ± 102.0 × 10^3/μL, $p < 0.001$), and creatinine (0.9 ± 0.3 mg/dL *vs.* 1.4 ± 1.8 mg/dL, $p < 0.001$). MACCE (27.6% *vs.* 29.9%, $p > 0.999$) and major bleeding (3.4% *vs.* 1.5%, $p = 0.359$) were similar.

In the female cohort (n = 571), the 2.5 mg group (n = 23) had higher age at PCI (81.0 ± 7.1 *vs.* 72.0 ± 10.6, $p < 0.001$), lower body weight (46.2 ± 7.2 kg *vs.* 54.6 ± 12.3 kg, $p < 0.001$), lower BMI (20.5 ± 3.1 *vs.* 23.9 ± 4.7, $p < 0.001$), higher prevalence of active malignancy (17.4% *vs.* 7.5%, $p = 0.014$), and more frequent antiplatelet (87.0% *vs.* 59.1%, $p = 0.008$) and anticoagulant therapy (17.4% *vs.* 4.4%, $p = 0.022$), than the 3.75 mg group (n = 548). Laboratory data showed lower hemoglobin (11.0 ± 1.5 g/dL *vs.* 11.8 ± 1.5 g/dL, $p = 0.019$) and platelet counts (55.8 ± 77.9 × 10^3/μL *vs.*

Table 4. Sub-analysis by renal function (eGFR)

Variables	eGFR > 30 mL/min/1.73 m^2 (n = 2,371)			eGFR ≤ 30 mL/min/1.73 m^2 (n = 244)		
	3.75 mg (n = 2,329)	2.5 mg (n = 50)	p-value	3.75 mg (n = 242)	2.5 mg (n = 2)	p-value
Characteristics						
Female	455 (19.5%)	22 (44.0%)	< 0.001	65 (26.9%)	1 (50.0%)	0.469
Age, years	67.4 ± 11.3	78.2 ± 8.3	< 0.001	70.2 ± 10.5	82.5 ± 6.4	0.216
Height, cm	163.2 ± 9.0	157.8 ± 8.9	< 0.001	161.0 ± 9.1	154.5 ± 0.7	< 0.001
Weight, kg	65.3 ± 13.2	55.4 ± 11.1	< 0.001	62.3 ± 13.7	54.3 ± 8.1	0.392
BMI, kg/m^2	24.4 ± 3.9	22.1 ± 3.2	< 0.001	23.9 ± 4.5	22.8 ± 3.6	0.731
Smoking	1,502 (64.5%)	24 (48.0%)	0.016	144 (59.5%)	0 (0.0%)	0.159
Weight ≤ 50 kg	262 (11.2%)	18 (36.0%)	< 0.001	44 (18.2%)	1 (50.0%)	0.355
Past medical history						
PCI	271 (11.6%)	9 (18.0%)	0.181	35 (14.5%)	0 (0.0%)	> 0.999
CABG	63 (2.7%)	5 (10.0%)	0.013	17 (7.0%)	0 (0.0%)	> 0.999
Myocaridal infarction	378 (16.2%)	6 (12.0%)	0.560	27 (11.2%)	0 (0.0%)	> 0.999
Heart failure	85 (3.6%)	4 (8.0%)	0.116	37 (15.3%)	1 (50.0%)	0.289
Stroke	117 (5.0%)	7 (14.0%)	0.014	31 (12.8%)	0 (0.0%)	> 0.999
Complications						
Diabetes mellitus	918 (39.4%)	22 (44.0%)	0.562	120 (49.6%)	0 (0.0%)	0.498
Dyslipidemia	1,864 (80.0%)	34 (68.0%)	0.046	161 (66.5%)	2 (100.0%)	> 0.999
Hypertension	1,856 (79.7%)	40 (80.0%)	> 0.999	207 (85.5%)	2 (100.0%)	> 0.999
Peripheral arterial disease	60 (2.6%)	5 (10.0%)	0.014	21 (8.7%)	0 (0.0%)	> 0.999
Atrial fibrillation	54 (2.3%)	2 (4.0%)	0.332	10 (4.1%)	1 (50.0%)	0.089
Hemodialysis	10 (0.4%)	0 (0.0%)	> 0.999	97 (40.1%)	1 (50.0%)	> 0.999
Active maligancy	216 (9.3%)	9 (18.0%)	0.007	282 (11.6%)	1 (50.0%)	0.233
Medications						
Antiplatelet	1,443 (62.0%)	42 (84.0%)	0.001	157 (64.9%)	2 (100.0%)	0.544
Anticoagulant	84 (3.6%)	13 (26.0%)	< 0.001	13 (5.4%)	1 (50.0%)	0.112
Statin	437 (18.8%)	15 (30.0%)	0.066	48 (19.8%)	1 (50.0%)	0.362
Antihypertensive drug	802 (34.4%)	11 (22.0%)	0.071	98 (40.5%)	0 (0.0%)	0.517
Laboratory variables						
Hemoglobin, g/dL	13.3 ± 1.7	11.9 ± 1.7	< 0.001	10.9 ± 1.7	12.7 ± 2.4	0.484
Platelet, 10^3/μL	108.0 ± 103.6	36.6 ± 55.4	< 0.001	103.6 ± 98.5	15.5 ± 1.8	< 0.001
Creatinin, mg/dL	0.9 ± 0.2	0.8 ± 0.2	0.201	5.6 ± 3.2	4.2 ± 3.2	0.643
PCI						
ACS	1,186 (50.9%)	18 (36.0%)	0.045	117 (48.3%)	1 (50.0%)	> 0.999
CCS	1,142 (49.0%)	32 (64.0%)		125 (51.7%)	1 (50.0%)	
Cardiovascular events						
MACCE	649 (27.9%)	12 (24.0%)	0.634	95 (39.3%)	0 (0.0%)	0.523
Non-fatal myocardial infarction	49 (2.1%)	0 (0.0%)	0.625	7 (2.9%)	0 (0.0%)	> 0.999
Non-fatal stroke	24 (1.0%)	3 (6.0%)	0.018	4 (1.7%)	0 (0.0%)	> 0.999
Cardiovascular death	33 (1.4%)	0 (0.0%)	> 0.999	17 (7.0%)	0 (0.0%)	> 0.999
Coronary revasculization	557 (23.9%)	9 (18.0%)	0.403	71 (29.3%)	0 (0.0%)	> 0.999
Major bleeding	31 (1.3%)	3 (6.0%)	0.033	6 (2.5%)	1 (50.0%)	0.057

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

119.5 ± 106.5 × 10^3/μL, p < 0.001). Women in the 2.5 mg group had higher rates of non-fatal stroke (8.7% *vs.* 1.3%, p = 0.047) and major bleeding (13.0% *vs.* 1.3%, p = 0.006) than those in the 3.75 mg group.

3.8. Sub-analysis by antithrombotic drugs

Patients receiving prasugrel were analyzed based on concomitant use of other antithrombotic drugs, as these agents (antiplatelet drugs and/or anticoagulants) are associated with MACCE and bleeding (Table 6). Among patients on antithrombotic therapy in addition to prasugrel (n = 1,485), the 2.5 mg group (n = 37) had a lower rate of antiplatelet agent use (91.9% *vs.* 99.3%, p = 0.003) and a higher rate of anticoagulant use (35.1% *vs.* 7.3%, p < 0.001) than the 3.75 mg group (n = 1,448). Triple therapy was administered in 95 and 10 patients in the 3.75 mg (6.6%) and 2.5 mg (27.0%) groups, respectively. With antithrombotic therapy, the incidence of MACCE (29.7% *vs.* 26.7%, p = 0.708) and coronary revascularization (24.3% *vs.* 23.1%, p = 0.845) was comparable between groups. However, the 2.5 mg group had higher rates of major bleeding than the 3.75 mg group (10.8% *vs.* 1.5%, p = 0.003).

In prasugrel monotherapy, the 2.5 mg group had significantly fewer MACCE events (6.7% *vs.* 32.8%,

Table 5. Sub-analysis by sex

Variables	Male (n = 2,180)			Female (n = 571)		
	3.75 mg (n = 2,151)	2.5 mg (n = 29)	p-value	3.75 mg (n = 548)	2.5 mg (n = 23)	p-value
Characteristics						
Age, years	66.6 ± 11.2	76.3 ± 8.6	< 0.001	72.0 ± 10.6	81.0 ± 7.1	< 0.001
Height, cm	166.0 ± 6.7	163.7 ± 4.6	0.011	150.8 ± 6.4	150.0 ± 6.4	0.567
Weight, kg	67.7 ± 12.9	62.7 ± 7.4	0.001	54.6 ± 12.3	46.2 ± 7.2	< 0.001
BMI, kg/m^2	24.5 ± 4.0	23.4 ± 2.6	0.032	23.9 ± 4.7	20.5 ± 3.1	< 0.001
Smoking	1,603 (74.5%)	19 (65.5%)	0.196	123 (22.4%)	5 (21.7%)	> 0.999
Weight ≤ 50 kg	112 (5.2%)	2 (6.9%)	0.826	210 (38.3%)	17 (73.9%)	0.004
Past medical history						
PCI	255 (11.9%)	7 (24.1%)	0.075	55 (10.0%)	2 (8.7%)	> 0.999
CABG	69 (3.2%)	3 (10.3%)	0.069	14 (2.6%)	2 (8.7%)	0.133
Myocaridal infarction	350 (16.3%)	5 (17.2%)	0.804	61 (11.1%)	1 (4.3%)	0.497
Heart failure	89 (4.1%)	3 (10.3%)	0.122	36 (6.6%)	2 (8.7%)	0.661
Stroke	1,161 (5.4%)	4 (13.8%)	0.073	34 (6.2%)	3 (13.0%)	0.183
Complications						
Diabetes mellitus	873 (40.6%)	12 (41.4%)	> 0.999	221 (40.3%)	10 (43.5%)	0.831
Dyslipidemia	1,700 (79.0%)	22 (75.9%)	0.642	427 (77.9%)	14 (60.9%)	0.067
Hypertension	1,695 (78.8%)	22 (75.9%)	0.645	445 (81.2%)	20 (87.0%)	0.781
Peripheral arterial disease	64 (3.0%)	4 (13.8%)	0.014	18 (3.3%)	1 (4.3%)	0.568
Atrial fibrillation	69 (3.2%)	2 (6.9%)	0.245	9 (1.6%)	1 (4.3%)	0.341
Hemodialysis	92 (4.3%)	0 (0.0%)	0.633	25 (4.6%)	1 (4.3%)	> 0.999
Active maligancy	225 (10.5%)	6 (20.7%)	0.078	41 (7.5%)	4 (17.4%)	0.012
Medications						
Antiplatelet	1,281 (59.6%)	24 (82.8%)	0.012	324 (59.1%)	20 (87.0%)	0.008
Anticoagulant	74 (3.4%)	10 (34.5%)	< 0.001	24 (4.4%)	4 (17.4%)	0.022
Statin	389 (18.1%)	9 (31.0%)	0.088	96 (17.5%)	7 (30.4%)	0.160
Antihypertensive drug	715 (33.2%)	4 (13.8%)	0.028	186 (33.9%)	7 (30.4%)	0.825
Laboratory variables						
Hemoglobin, g/dL	13.4 ± 1.8	12.7 ± 1.5	0.021	11.8 ± 1.5	11.0 ± 1.5	0.019
Platelet, 10^3/μL	104.6 ± 102.0	19.9 ± 6.2	< 0.001	119.5 ± 106.5	55.8 ± 77.9	< 0.001
Creatinin, mg/dL	1.4 ± 1.8	0.9 ± 0.3	< 0.001	1.1 ± 1.4	1.0 ± 1.2	0.541
eGFR, mL/min/1.73 m^2	64.6 ± 24.7	63.6 ± 15.5	0.731	60.4 ± 25.2	61.3 ± 22.1	0.842
eGFR ≤ 30 mL/min/1.73 m^2	177 (8.2%)	1 (3.4%)	0.448	65 (11.9%)	1 (4.3%)	0.373
PCI						
ACS	1,089 (50.6%)	5 (17.2%)	< 0.001	277 (50.5%)	14 (60.9%)	0.397
CCS	1,061 (49.3%)	24 (82.8%)		271 (49.5%)	9 (39.1%)	
Cardiovascular events						
MACCE	644 (29.9%)	8 (27.6%)	> 0.999	161 (29.4%)	4 (17.4%)	0.249
Non-fatal myocardial infarction	46 (2.1%)	0 (0.0%)	> 0.999	12 (2.2%)	0 (0.0%)	> 0.999
Non-fatal stroke	24 (1.1%)	1 (3.4%)	0.286	7 (1.3%)	2 (8.7%)	0.047
Cardiovascular death	41 (1.9%)	0 (0.0%)	> 0.999	12 (2.2%)	0 (0.0%)	> 0.999
Coronary revasculization	548 (25.5%)	7 (24.1%)	> 0.999	134 (24.5%)	2 (8.7%)	0.130
Major bleeding	32 (1.5%)	1 (3.4%)	0.359	7 (1.3%)	3 (13.0%)	0.006

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

p = 0.048) and coronary revascularization procedures (0.0% *vs.* 27.0%, p = 0.016) than the 3.75 mg group. No major bleeding was observed with 2.5 mg prasugrel monotherapy. Among patients receiving prasugrel 2.5 mg plus concomitant antithrombotic therapy, serious bleeding occurred in four patients: two received antiplatelet therapy, one received anticoagulant therapy, and one received both (triple therapy).

3.9. Factors associated with prasugrel 2.5 mg

Factors associated with prasugrel 2.5 mg were analyzed using univariate logistic regression (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=117*). Associated factors included female sex (OR = 3.115, 95% CI = 1.770–5.405, p < 0.001), older age at PCI (OR = 1.122, 95% CI = 1.085–1.163, p < 0.001), short height (OR = 1.060, 95% CI = 1.031–1.091, p < 0.001), low body weight (OR = 1.067, 95% CI = 1.042–1.094, p < 0.001), low BMI (OR = 1.192, 95% CI = 1.099–1.294, p < 0.001), non-smoking (OR = 0.468, 95% CI = 0.268–0.812, p = 0.007), prior CABG surgery (OR = 3.341, 95% CI = 1.138–7.859, p = 0.012), history of stroke (OR = 2.409,

Table 6. Sub-analysis by antithrombotic drugs

Variables	Antithrombotic drugs (n = 1,485)			Prasugrel only (n = 1,436)		
	3.75 mg (n = 1,448)	2.5 mg (n = 37)	p-value	3.75 mg (n = 1,421)	2.5 mg (n = 15)	p-value
Characteristics						
Female	276 (19.1%)	15 (40.5%)	0.003	272 (19.1%)	8 (53.3%)	0.008
Age, years	68.7 ± 11.0	78.2 ± 6.9	< 0.001	66.9 ± 10.6	78.7 ± 7.1	0.001
Height, cm	162.5 ± 9.0	158.3 ± 9.0	0.008	163.4 ± 9.1	156.0 ± 8.2	0.567
Weight, kg	64.3 ± 12.6	56.4 ± 10.1	< 0.001	65.7 ± 13.8	52.9 ± 13.0	0.002
BMI, kg/m^2	24.2 ± 3.7	22.4 ± 3.0	< 0.001	24.5 ± 4.1	21.4 ± 3.5	0.004
Smoking	942 (65.1%)	17 (45.9%)	0.022	883 (62.1%)	7 (46.7%)	0.185
Weight ≤ 50 kg	163 (12.6%)	12 (32.4%)	0.002	157 (11.7%)	7 (46.7%)	< 0.001
Past medical history						
PCI	219 (15.1%)	6 (16.2%)	0.835	122 (8.6%)	3 (20.0%)	0.273
CABG	55 (3.8%)	5 (13.5%)	0.039	33 (2.3%)	0 (0.0%)	> 0.999
Myocaridal infarction	258 (17.8%)	3 (8.1%)	0.283	181 (12.7%)	3 (20.0%)	0.513
Heart failure	93 (6.4%)	4 (10.8%)	0.333	37 (2.6%)	1 (6.7%)	0.427
Stroke	109 (7.5%)	5 (13.5%)	0.239	64 (4.5%)	2 (13.3%)	0.276
Complications						
Diabetes mellitus	588 (40.6%)	16 (43.2%)	0.898	574 (40.4%)	6 (40.0%)	> 0.999
Dyslipidemia	1,114 (76.9%)	25 (67.6%)	0.268	1,118 (78.7%)	11 (73.3%)	0.602
Hypertension	1,190 (82.2%)	32 (86.5%)	0.680	1,067 (75.1%)	10 (66.7%)	0.482
Peripheral arterial disease	59 (4.1%)	4 (10.8%)	0.036	35 (2.5%)	1 (6.7%)	0.392
Atrial fibrillation	39 (2.7%)	3 (8.1%)	0.084	44 (3.1%)	0 (0.0%)	> 0.999
Hemodialysis	61 (4.2%)	1 (2.7%)	> 0.999	71 (5.0%)	0 (0.0%)	> 0.999
Active maligancy	199 (13.7%)	8 (21.6%)	0.222	95 (6.7%)	2 (13.3%)	0.017
Medications						
Antiplatelet	1,438 (99.3%)	34 (91.9%)	0.003	0 (0.0%)	0 (0.0%)	> 0.999
Anticoagulants	105 (7.3%)	13 (35.1%)	< 0.001	0 (0.0%)	0 (0.0%)	> 0.999
Statin	401 (27.7%)	9 (24.3%)	0.714	87 (6.1%)	3 (20.0%)	0.063
Antihypertensive drug	637 (44.0%)	6 (16.2%)	< 0.001	168 (11.8%)	1 (6.7%)	> 0.999
Laboratory variables						
eGFR, mL/min/1.73 m^2	62.4 (24.9)	58.5 (18.4)	0.226	65.3 (24.8)	72.6 (15.0)	0.081
Hemoglobin, g/dL	13.0 (1.8)	12.0 (1.6)	< 0.001	13.2 (1.9)	12.5 (1.9)	0.165
Platelet, 10^3/μL	100.6 (100.9)	21.7 (8.2)	< 0.001	128.0 (106.3)	73.3 (97.7)	0.049
Creatinin, mg/dL	1.4 (1.8)	1.1 (1.0)	0.050	1.3 (1.7)	0.7 (0.2)	< 0.001
eGFR ≤ 30 mL/min/1.73 m^2	136 (10.2%)	2 (5.4%)	0.576	106 (8.5%)	0 (0.0%)	0.630
PCI						
ACS	655 (45.2%)	12 (32.4%)	0.134	764 (53.8%)	7 (46.7%)	0.612
CCS	793 (54.8%)	25 (67.6%)		656 (46.2%)	8 (53.3%)	
Cardiovascular events						
MACCE	387 (26.7%)	11 (29.7%)	0.708	466 (32.8%)	1 (6.7%)	0.048
Non-fatal myocardial infarction	18 (1.2%)	0 (0.0%)	> 0.999	47 (3.3%)	0 (0.0%)	> 0.999
Non-fatal stroke	15 (1.0%)	2 (5.4%)	0.065	18 (1.3%)	1 (6.7%)	0.182
Cardiovascular death	33 (2.3%)	0 (0.0%)	> 0.999	24 (1.7%)	0 (0.0%)	> 0.999
Coronary revasculization	335 (23.1%)	9 (24.3%)	0.845	383 (27.0%)	0 (0.0%)	0.016
Major bleeding	21 (1.5%)	4 (10.8%)	0.003	20 (1.4%)	0 (0.0%)	> 0.999

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

95% CI = 0.980–5.088, p = 0.034), peripheral artery disease (OR = 2.971, 95% CI = 1.013–6.975, p = 0.024), active malignancy (OR = 2.196, 95% CI = 1.027–4.275, p = 0.029), antiplatelet use (OR = 3.658, 95% CI = 1.814–8.416, p < 0.001), anticoagulant use (OR = 9.069, 95% CI = 4.630–16.855, p < 0.001), statins use (OR = 1.878, 95% CI = 1.008–4.275, p = 0.038), low hemoglobin (OR = 1.350, 95% CI = 1.171–1.553, p < 0.001) and low platelet count (OR = 1.013, 95% CI = 1.008–3.350, p < 0.001). No association was observed with eGFR (OR = 0.998, 95% CI = 0.987–1.009, p = 0.735).

Multivariate logistic regression analysis (Table 7) identified the following factors independently associated with prasugrel 2.5 mg: female sex (OR = 2.967, 95% CI = 1.126–7.874, p < 0.001), older age at PCI (OR = 1.121, 95% CI = 1.073–1.175, p < 0.001), anticoagulant therapy (OR = 10.580, 95% CI = 4.632–23.748, p < 0.001), statin use (OR = 2.152, 95% CI = 1.057–4.269, p = 0.030), absence of antihypertensive drugs (OR = 3.831, 95% CI = 1.815–8.772, p < 0.001), and thrombocytopenia (OR = 1.014, 95% CI = 1.009–1.022, p < 0.001).

Table 7. Analysis of factors associated with 2.5 mg of prasugrel by multivariate logistic regression models

Variables	Multivariate logistic regression analysis		
	OR	95% CI	*p*-value
Characteristic			
Female	2.966	1.125–7.886	0.028
Age, years	1.121	1.073–1.175	< 0.001
Height, cm	0.946	0.793–1.157	0.569
Weight, kg	1.115	0.845–1.412	0.414
BMI, kg/m^2	0.708	0.388–1.398	0.299
Complications			
Atrial fibrillation	0.721	0.133–2.921	0.672
Medications			
Antiplatelet	2.122	0.971–5.195	0.075
Anticoagulant	10.580	4.632–23.748	< 0.001
Statin	2.152	1.057–4.269	0.030
Antihypertensive drug	0.261	0.114–0.551	< 0.001
Laboratory variables			
eGFR, mL/min/1.73 m^2	1.012	0.992–1.029	0.191
Hemoglobin, g/dL	0.953	0.770–1.180	0.656
Platelet, 10^3/μL	0.986	0.978–0.991	< 0.001
Creatinin, mg/dL	0.848	0.406–1.237	0.526

Abbreviations: OR, odds ratio; CI, confidence interval. BMI, body mass index; eGFR, estimated glomerular filtration rate.

3.10. Factors associated with MACCE and major bleeding

Multivariate Cox proportional hazard models for MACCE and major bleeding are presented in Table 8. MACCE risk decreased with anticoagulant (HR = 0.447, 95% CI = 0.244–0.819, p = 0.009), antihypertensive use (HR = 0.814, 95% CI = 0.673–0.984, p = 0.033), and higher eGFR (HR = 0.995, 95% CI = 0.990–1.000, p = 0.042), but increased with higher platelet count (HR = 1.002, 95% CI = 1.001–1.002, p < 0.001). Low platelet counts were associated with a higher risk of major bleeding (HR = 1.007, 95% CI = 1.002–1.012, p = 0.010).

4. Discussion

For patients with ACS undergoing PCI, guidelines from Europe and the United States recommend the more potent prasugrel or ticagrelor, rather than clopidogrel, as the P2Y12 receptor inhibitor of choice for dual antiplatelet therapy (DAPT) combinations (*16,17*). Modulation of antiplatelet therapy is important because bleeding is a critical issue (*18*). The STOPDAPT-2 ACS study demonstrated that 1-month DAPT was more effective than 12-month DAPT (*19*). The 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guidelines for the management of ACS recommend 5 mg of prasugrel daily as the MD for non-ST-segment elevation ACS or ST-segment elevation myocardial infarction in patients with body weight < 50 kg or age > 75 years (*17*).

Prasugrel 20 mg LD/3.75 mg MD was associated with increased bleeding risk compared with clopidogrel in patients with ACS undergoing PCI in Japan (*20,21*). Conversely, prasugrel 15 mg LD/3.75 mg MD was well tolerated and achieved a more rapid, larger, and consistent antiplatelet effect than clopidogrel in Japanese patients with coronary artery disease undergoing PCI, while prasugrel 10 mg LD/2.5 mg MD showed almost the same inhibition of platelet aggregation as the standard clopidogrel dose (*22*).

In this study, patients weighing ≤ 50 kg accounted for 11.6%, yet only 1.8% received prasugrel 2.5 mg after PCI (Table 1). Most physicians considered 3.75 mg of prasugrel safe and did not feel the need for dose reduction.

The 2.5 mg group included more women than the 3.75 mg group, which may be associated with older age, shorter height, lower body weight, lower BMI, and nonsmoking status. The higher rates of CABG, stroke, and peripheral arterial disease in the 2.5 mg group indicated progression of atherosclerosis. Frequent use of antiplatelets, anticoagulants, and statins also reflected higher cardiovascular risk. Low hemoglobin and platelet counts may have influenced the choice of the 2.5 mg dose.

Prasugrel 2.5 mg did not increase MACCE compared to the 3.75 mg group, which may support its selection (Table 1). However, nonfatal strokes were significantly more common in the 2.5 mg group, suggesting that 3.75 mg may be more appropriate for patients with a history of stroke or TIA. In the 2.5 mg group, major bleeding occurred only with concomitant antithrombotic drugs, indicating that such combinations should be avoided if possible. No major bleeding occurred in the 2.5 mg prasugrel monotherapy group (Table 6).

According to Kaplan–Meier analysis, MACCE occurred within 1 year in the 2.5 mg group, whereas it increased steadily in the 3.75 mg group (Figure 2), suggesting that dose reduction may be appropriate after

Table 8. Analysis of factors associated with MACCE and major bleeding by multivariate logistic regression models

Variables	MACCE			Major bleeding		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Dose						
2.5 mg	0.906	0.492–1.670	0.752	2.246	0.664–7.593	0.193
Characteristic						
Female	1.015	0.773–1.331	0.916	1.107	0.347–3.534	0.863
Age, years	1.004	0.996–1.013	0.328	0.991	0.951–1.032	0.657
Height, cm	1.026	0.975–1.078	0.324	0.988	0.800–1.221	0.910
Weight, kg	0.973	0.917–1.034	0.381	1.027	0.773–1.365	0.855
BMI, kg/m^2	1.087	0.926–1.274	0.307	0.805	0.381–1.699	0.569
Complication						
Atrial fibrillation	1.560	0.994–2.448	0.053	0.708	0.086–5.808	0.748
Medications						
Antiplatelet	1.011	0.857–1.191	0.900	1.090	0.520–2.285	0.820
Anticoagulant	0.447	0.244–0.819	0.009	2.275	0.672–7.707	0.187
Statin	0.845	0.668–1.069	0.160	1.348	0.558–3.253	0.507
Antihypertensive drug	0.814	0.673–0.984	0.033	0.437	0.170–1.122	0.085
Laboratory variables						
eGFR, mL/min/1.73 m^2	0.995	0.990–1.000	0.042	0.990	0.967–1.012	0.365
Hemoglobin, g/dL	1.005	0.956–1.058	0.834	0.931	0.741–1.170	0.539
Platelet, 10^3/μL	1.002	1.001–1.002	< 0.001	0.993	0.988–0.998	0.010
Creatinin, mg/dL	0.986	0.928–1.046	0.633	0.884	0.633–1.235	0.469

Abbreviations: HR, hazard ratio; CI, confidence interval. BMI, body mass index; eGFR, estimated glomerular filtration rate; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization).

1 year. Most major bleeding events occurred within 6 months, highlighting the need for close monitoring during this period.

MACCE occurs more frequently in ACS than in CCS in Japan (*2,3*). Prasugrel 2.5 mg was administered in only 0.97% and 2.22% of patients with ACS and CCS, respectively. MACCE did not increase in the 2.5 mg group compared to the 3.75 mg group in either ACS or CCS (Table 2). Use of 2.5 mg prasugrel was associated with a significant increase in major bleeding in ACS but was non-significant in CCS.

Although the prasugrel package insert states that 2.5 mg may be considered for patients weighing ≤ 50 kg, in actual clinical practice, only 5.6% of patients in the group received a 2.5 mg dose (Table 3), most being female. The incidence of major bleeding was high (15.8%), requiring caution even with the reduced dose.

In patients with eGFR ≤ 30 ml/min/1.73 m^2, only 0.82% received prasugrel 2.5 mg, lower than the 1.8% in the overall population, indicating that dose reduction based on renal function is rarely implemented in Japan (Table 4). Only two patients with severe renal impairment were in the 2.5 mg group, precluding statistical analysis.

The background characteristics of men and women were similar, but among women, the 2.5 mg group had more non-fatal strokes and major bleeding than the 3.75 mg group (Table 5).

Univariate and multivariate logistic regression and Cox hazard model analyses (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=117*, and Table 7) identified multiple factors associated with the 2.5 mg dose. Female sex and older age were consistent with previous reports (*23*). Anticoagulant or statin use, absence of antihypertensive therapy, and thrombocytopenia were also important factors.

Multivariate Cox proportional hazards analysis showed that MACCE decreased with anticoagulant or antihypertensive use and higher eGFR, but increased with higher platelet counts (Table 8). Prasugrel dose did not affect MACCE, and only platelet count was a significant factor for major bleeding.

This study had some limitations. First, it was a retrospective observational study, and dose selection bias may have occurred. Understanding the use of prasugrel 2.5 mg in East Asia is important due to reported bleeding tendencies. Second, the small number of patients in the 2.5 mg group limited statistical power in some sub-analyses. Nevertheless, MACCE and major bleeding rates were detected, and logistic regression analyses identified several factors associated with prasugrel dose selection. Third, the study population was limited to Japanese patients, and the standard prasugrel dose in Japan was lower than that in other countries. Therefore, these results cannot be directly applied to other ethnicities; however, they demonstrate the potential use of prasugrel 2.5 mg in selected patients.

5. Conclusions

In summary, since MACCE did not increase in the 2.5 mg group compared with the 3.75 mg group, prasugrel

2.5 mg may be considered to reduce major bleeding in patients with low body weight, older patients, women, patients receiving concomitant anticoagulants, or those with low platelet counts.

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Prognostic comparison between osteoblastic and osteolytic metastases in prostate cancer

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Abstract: Over 80% of patients develop bone metastases in the advanced stages of prostate cancer, resulting in a poor prognosis. To date, no study has explored the relationship between the type of bone metastasis and patient outcomes. The objective of this study was to compare the clinical features and prognoses of patients with osteoblastic and osteolytic bone metastases. Among the 63 patients diagnosed with bone metastases from prostate cancer at our institution between May 2011 and September 2023, 51 were classified as having osteoblastic metastases and 12 as having osteolytic metastases based on imaging findings. Overall survival was analyzed using Kaplan–Meier survival curves, and differences between groups were assessed using the log-rank test. Clinical parameters were compared using the Mann–Whitney *U* test. Univariate and multivariate Cox proportional hazards analyses were conducted to identify the prognostic factors. No significant differences were observed between the osteoblastic and osteolytic groups in terms of clinical or laboratory parameters, except for a higher platelet count in the osteoblastic group ($p = 0.0181$). The five-year overall survival rate was significantly higher in the osteoblastic group than in the osteolytic group (49.5% *vs.* 30.0%, $p = 0.0437$), with median survival times of 59 months and 38.5 months, respectively. In both univariate and multivariate Cox analyses, the type of bone metastasis was the only factor significantly associated with increased hazard ratios. Patients with osteolytic bone metastases from prostate cancer have a markedly lower five-year overall survival than those with osteoblastic metastases.

***Keywords*:** bone metastases, osteoblastic, osteolytic, prostate cancer

1. Introduction

Prostate cancer (PCa) is the second most prevalent cancer among men, after lung cancer, and accounts for 3.8% of all cancer-related deaths, making it the fifth leading cause of cancer-related mortality worldwide. According to EUROCARE-5, the 5-year survival rate for patients with PCa diagnosed between 2003 and 2007 was 83% in Europe (*1*). In Japan, the five-year overall survival (OS) rate of patients treated with primary androgen deprivation therapy between 2001 and 2003 was 75.6% (*2*). Overall, these estimates indicate that the prognosis of PCa is relatively good.

However, the prognosis of patients with metastatic PCa remains poor. The adjusted 5-year OS rate for patients with metastatic castration-resistant PCa remained low at only 35% (95% confidence interval [CI]: 31–40%) between 2017 and 2020, showing only a modest increase from 26% (95% CI: 25–28%) between 2008 and 2012 (*3*). In advanced PCa, over 80% of patients develop metastases in the bone, reflecting the strong affinity of PCa for bone tissue (*4,5*). Notably, bone metastasis is recognized as an indicator of poor prognosis according to the Surveillance, Epidemiology, and End Results (SEER) database (*6*).

Depending on the roles of osteoblasts and osteoclasts in the formation of bone-metastatic lesions, bone metastases can be categorized into osteoblastic, osteolytic, or mixed types. Growth factors released by osteoclasts during bone resorption, including transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), bone morphogenetic protein (BMP), and platelet-derived growth factor (PDGF), promote osteoblast differentiation and induce bone formation. Tumor cells secrete osteoclast-activating factors, including macrophage colony-stimulating

factor (M-CSF), receptor activator of nuclear factor-kappa B ligand (RANKL), and parathyroid hormone-related protein (PTHrP) to promote bone destruction. The balance of interactions between osteoclasts and osteoblasts determines the morphology of bone metastases (*7*).

While patients with a Gleason score (GS) ≥ 8 are reportedly more likely to develop osteolytic or mixed bone metastases compared with those with GS ≤ 7 (*8*), no previous research has explored the association between the bone metastasis types and the prognosis. Therefore, in this study, we classified patients with bone-metastatic PCa treated at our institution into osteoblastic, osteolytic, or mixed bone metastasis groups and compared their clinical features.

2. Patients and Methods

2.1. Patient selection and classification of bone metastases

We extracted patients from the medical records whose radiology reports contained the terms osteolytic metastasis or osteoblastic metastasis and seventy-four patients diagnosed with PCa with bone metastases at our hospital between May 2011 and September 2023 were included in this study. After excluding 11 patients with missing data, the clinical data of 63 patients were analyzed (Figure 1).

One of the excluded patients showed uptake on bone scintigraphy; however, bone metastasis from PCa was clinically ruled out. Another patient had been referred to our hospital for an unrelated condition, during which a CT scan incidentally revealed bone metastases from previously diagnosed and treated PCa at another institution. We did not treat PCa or metastasis ourselves, and no further clinical information was available. The third excluded patient was referred to our hospital for treatment but was lost to follow-up after the initial visit. Among the remaining eight cases, one was excluded from the analysis owing to the absence of PSA data at the time of bone metastasis diagnosis, two due to insufficient laboratory data aside from PSA, and the remaining five due to a lack of pathological findings.

Patients were categorized into one of the following groups based on bone scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI) findings: osteoblastic, osteolytic, or mixed metastases. Of the 63 patients, 51 were classified as osteoblastic, 7 as osteolytic, and 5 as mixed-type.

Patients with mixed-type metastases were included in the osteolytic group to assess the impact of osteolytic metastasis on PCa. Consequently, 51 patients from the osteoblastic group and 12 patients from the osteolytic group were included in the analysis.

2.2. Ethical approval

Ethical approval for this study was obtained from the Institutional Review Board of NTT Medical Center Tokyo, which approved the researchs protocol (Approval No. 22-102). Informed consent was obtained from all participants through an opt-out method. All procedures were conducted in accordance with the principles of the Declaration of Helsinki (2013 revision).

2.3. Statistical analysis

OS was analyzed for 63 patients using Kaplan–Meier survival curves and the log-rank test. Clinical parameters, including age, prostate-specific antigen (PSA) levels, GS, and other laboratory test values, were compared between the osteoblastic and osteolytic groups using the Mann–Whitney *U* test.

To identify factors that influence the 5-year survival rate, both univariate and multivariate Cox proportional hazards analyses were performed. In the multivariate model, five clinically relevant variables were included: PSA level at the time of bone metastasis, International

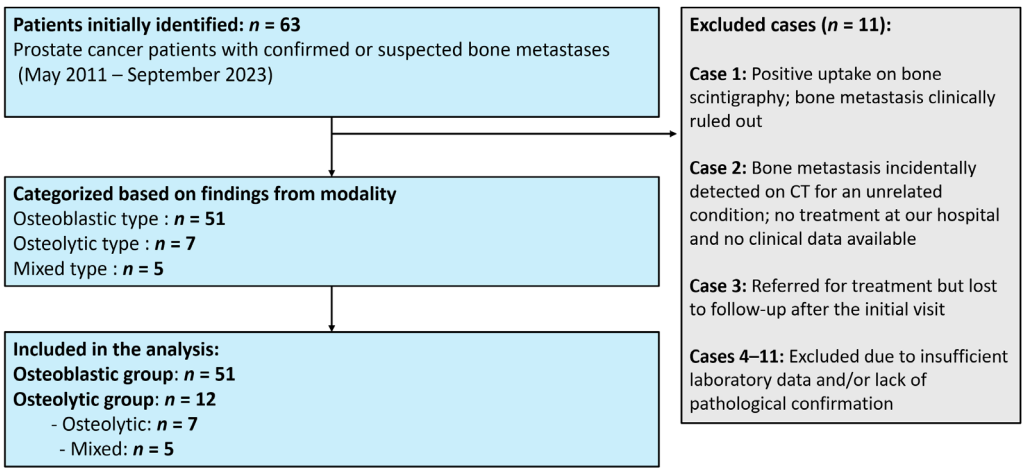


Figure 1. Inclusion and exclusion criteria of patient recruitment.

Society of Urological Pathology (ISUP) grade, extent of disease (EOD) score, age at bone metastasis, and bone metastasis type.

A total of 63 patients (51 with osteoblastic and 12 with osteolytic metastases) were analyzed, with 44 events observed. According to the commonly accepted event-per-variable (EPV) rule recommending at least 10 events per variable, the inclusion of four to five variables in the multivariate model was considered statistically appropriate and unlikely to result in model overfitting.

All the statistical analyses were performed using the EZR software. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical feature comparison

A total of 63 patients with bone-metastatic PCa were included in this study, with 51 (81.0%) classified as having osteoblastic lesions and 12 (19.0%) classified as having osteolytic or mixed lesions. There were no statistically significant differences in clinical parameters between the osteoblastic and osteolytic groups (Table 1).

In both groups, the median age at PCa diagnosis was 71 years. Likewise, there was no significant difference in the median age at bone metastasis between groups (71 and 73 years, respectively; $p = 0.269$). In both groups, a considerable number of patients had bone metastases at the time of PCa diagnosis. Furthermore, the interval between the diagnosis of PCa and bone metastasis did not differ significantly between the osteoblastic and osteolytic metastasis groups.

The median initial PSA level was 278 ng/mL in the osteoblastic group and 119.13 ng/mL in the osteolytic/mixed group ($p = 0.500$). PSA levels at bone metastasis were also similar between groups: 308 ng/mL in the osteoblastic group and 148.63 ng/mL in the osteolytic/mixed group ($p = 0.396$). The ISUP grade and clinical T stage distributions were similar between groups ($p = 0.672$ and 0.827, respectively).

Among laboratory parameters, platelet count was significantly lower in the osteolytic group than the osteoblastic group (median [interquartile range], 23.6 [19.65–30.15] *vs.* 18.75 [15.975–23.9] $\times 10^4/\mu L$, $p = 0.0181$).

3.2. Prognostic analysis

The five-year OS rate of patients with osteolytic metastases was notably lower than that of patients with osteoblastic metastases, at 30.0% (95% CI: 0.077–0.569) versus 49.5% (95% CI: 0.340–0.632), respectively ($p = 0.0437$). Furthermore, the median survival time was shorter in the osteolytic group, at 38.5 months (95% CI: 16–61 months), compared with 59 months (95% CI:

Table 1. Patient characteristics

Variables	Osteoblastic ($n = 51$)	Osteolytic ($n = 12$)	p-value
Age at diagnosis of PCa (years), median (IQR)	71 (66–74)	71 (67.5–76)	0.528
Age at bone metastases (years), median (IQR)	71 (67.5–75)	73 (69–78.25)	0.269
Initial PSA (ng/mL), median (IQR)	278 (32.4565–1240)	119.13 (55.175–381.75)	0.500
PSA at bone metastases (ng/mL), median (IQR)	308 (47.3065–1240)	148.63 (55.175–381.78)	0.396
ISUP Grade groups			0.672
Grade group 1–3, *n* (%)	5 (9.8%)	1 (8.3%)	
Grade group 4, *n* (%)	11 (21.6%)	2 (16.7%)	
Grade group 5, *n* (%)	35 (68.6%)	9 (75.0%)	
Clinical stage			
T stage			0.879
≤ cT2, *n* (%)	11 (21.6%)	3 (25.0%)	
T3, *n* (%)	27 (52.9%)	5 (41.7%)	
T4, *n* (%)	13 (25.4%)	4 (33.3%)	
N stage			0.769
N0, *n* (%)	23 (45.1%)	6 (50.0%)	
N1, *n* (%)	28 (54.9%)	6 (50.0%)	
EOD			0.0713
EOD1, *n* (%)	13 (25.5%)	2 (16.7%)	
EOD2, *n* (%)	13 (25.5%)	10 (83.3%)	
EOD3, *n* (%)	22 (43.1%)	0 (0%)	
EOD4, *n* (%)	3 (5.9%)	0 (0%)	
Laboratory findings at bone metastases			
LDH (IF) (IU/L), median (IQR)	202 (172.5–276)	196 (183.5–212)	0.436
ALP (IU/L), median (IQR)	459 (236.5–1100)	378.5 (270–574.5)	0.575
Ca (mg/dL), median (IQR)	9.2 (8.9–9.4)	9.4 (9.2–9.65)	0.0754
Alb (g/dL), median (IQR)	4.1 (3.7–4.3)	4.3 (4.075–4.425)	0.143
Hb (g/dL), median (IQR)	12.9 (11.75–14.5)	14.15 (12.575–15.9)	0.123
Plt ($\times 10^4/\mu L$), median(IQR)	23.6 (19.65–30.15)	18.75 (15.975–23.9)	0.0181

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; Hb, hemoglobin; EOD, extent of disease; ISUP, International Society of Urological Pathology; IQR, interquartile range; LDH, lactate dehydrogenase; PCa, prostate cancer; Plt, platelets; PSA, prostate-specific antigen.

41–115 months) in the osteoblastic group (Figure 2).

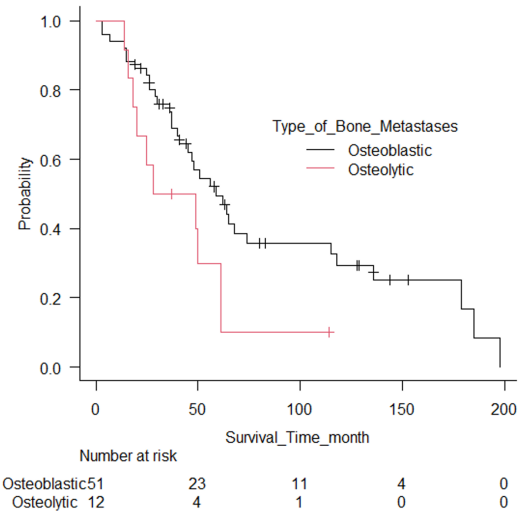
3.3. Results of Cox proportional hazards analyses

In the univariate Cox proportional hazards analysis, only bone metastasis type was significantly associated with OS (hazard ratio [HR] = 2.079; 95% CI: 1.002–4.317; p = 0.050) (Table 2).

A multivariate Cox proportional hazards analysis was performed, incorporating five clinically relevant factors: PSA level at the time of bone metastases, ISUP grade group, EOD, age at bone metastases, and bone metastases type. Consistent with the univariate analysis, only the bone metastasis type remained significantly associated with OS (HR = 2.334; 95% CI: 1.024–5.320; p = 0.044) (Table 2).

4. Discussion

Although osteoblastic lesions are typically observed in bone-metastatic PCa, bone formation (osteoblastic activity) and bone resorption (osteoclastic activity) coexist, with osteoclasts playing a critical role (*9*). Initially, bone metastases predominantly exhibit osteolytic activity, leading to bone destruction. The degradation process promotes tumor cell proliferation



Metastasis Type	*n*	5-YeaSurvival Rate	95% CI	Median Survival (months)	95% CI	*p* value
Osteoblastic	**51**	**0.495**	**0.340–0.632**	**59**	**41–115**	**0.0437**
Osteolytic	**12**	**0.3**	**0.077–0.569**	**38.5**	**16–61**	**–**

Figure 2. Kaplan–Meier curve for overall survival. The five-year overall survival rate was significantly higher in the osteoblastic group than in the osteolytic group.

Table 2. Univariate and multivariate analyses

Variable	Univariate HR (95% CI)	*p*-value	Multivariate HR (95% CI)	*p*-value
Age at diagnosis of PCa (years)	1.023 (0.974–1.073)	0.369	–	–
PSA at diagnosis of PCa (ng/mL)	1.000 (0.9997–1.000)	0.793	–	–
Age at bone metastases (years)	1.040 (0.990–1.093)	0.118	1.578 (0.795–3.13)	0.192
PSA at bone metastases (ng/mL)	1.000 (0.9998–1.000)	0.842	0.685 (0.345–1.363)	0.281
EOD score	1.042 (0.748–1.453)	0.807	1.644 (0.769–3.514)	0.2
ISUP Grade Group	1.189 (0.763–1.853)	0.444	1.051 (0.378–2.921)	0.925
T stage	0.843 (0.554–1.283)	0.426	–	–
N stage	0.767 (0.420–1.399)	0.387	–	–
Albumin at bone metastases (g/dL)	0.881 (0.549–1.414)	0.6	–	–
ALP at bone metastases (IU/L)	1.000 (1.000–1.001)	0.068	–	–
Hemoglobin at bone metastases (g/dL)	0.935 (0.803–1.088)	0.385	–	–
LDH at bone metastases (IU/L)	1.002 (0.9995–1.004)	0.133	–	–
Platelet count at bone metastases ($\times 10^4/\mu L$)	1.008 (0.973–1.045)	0.666	–	–
Corrected calcium at bone metastases (mg/dL)	1.008 (0.454–2.239)	0.984	–	–
Bone metastasis type (Osteolytic *vs.* Osteoblastic)	2.079 (1.002–4.317)	0.05	2.334 (1.024–5.32)	0.044

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; EOD, extent of disease; HR, hazard ratio; ISUP, International Society of Urological Pathology; LDH, lactate dehydrogenase; PCa, prostate cancer; Plt, platelets; PSA, prostate-specific antigen.

and stimulates osteoblast activation by releasing growth factors, such as TGF-β. This cascade initiates subsequent osteoblastic responses and new bone formation (*10*).

While RANKL-dependent signaling is predominant during the initial formation of bone metastases, subsequent progression may be driven by inflammatory signaling pathways involving factors such as interleukin (IL)-1β. For example, the expression of IL-1β is implicated in the progression of bone metastases (*11*) and promotes osteoclast differentiation and activation *via* RANKL-independent pathways (*12*). Osteoclasts co-cultured with PCa cells were shown to exhibit resistance to denosumab, accompanied by the activation of inflammatory signaling pathways (*13*). This mechanism aligns with clinical observations that denosumab prolongs the time to bone metastasis but does not improve OS (*14*). IL-1β–mediated activation of these pathways may lead to excessive osteoclast activity, thereby inhibiting the transition from bone resorption to bone formation, and clinically manifesting as an osteolytic metastatic phenotype.

In this cohort of patients with PCa and bone metastases, patients with osteolytic metastases exhibited a poorer prognosis than those with osteoblastic metastases. Although not statistically significant, patients with osteoblastic metastases tended to present with higher EOD scores at the time of diagnosis. Accordingly, osteolytic metastases may have a detrimental impact on survival, even when the extent of bone involvement is relatively limited.

A previous study reported that patients with osteolytic bone metastases more frequently presented with a GS of > 8 (*9*). In our cohort, we detected no statistically significant differences in GS between the two groups. Nevertheless, the association between osteolytic metastases and poor prognosis identified in this analysis was consistent with that reported in a previous study.

Notably, platelet counts were substantially lower in patients with osteoblastic metastasis. An increased platelet-to-lymphocyte ratio (PLR) may reflect systemic inflammation and cancer-related immunosuppression, both associated with poor prognosis (*15*). Interestingly, our results demonstrated the opposite trend in platelet counts, warranting further investigation.

The limitations of this study should be acknowledged. First, the relatively small sample size and the heterogeneity of treatment strategies among patients may have affected the robustness of the findings. To obtain more reliable and generalizable results, further studies with larger cohorts are warranted. Second, the diagnosis of bone metastases was evaluated qualitatively rather than quantitatively, and was not performed by a single radiologist; instead, different radiologists were involved, and the imaging modalities were not uniform, including bone scintigraphy, CT, and MRI examinations. Moreover, bone scintigraphy may have underestimated osteolytic metastases, and the potential impact of this limitation on the results cannot be excluded. Given that fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) reportedly has high sensitivity for detecting osteolytic metastases (*16*), a more accurate assessment may require PET-CT. Recent investigations have demonstrated favorable sensitivity and specificity of prostate-specific membrane antigen positron emission tomography/CT (PSMA-PET/CT) and MRI for detecting bone metastases (*17*). These modalities are expected to facilitate more comprehensive and accurate assessment.

Nonetheless, comparing survival outcomes based on the bone metastasis type in a real-world setting provides valuable insights.

In conclusion, our findings suggest that the presence of osteolytic metastases could serve as a prognostic factor for PCa. Given the relevance of IL-1β to resistance against docetaxel chemotherapy in patients with PCa (*18*), IL-1β overexpression, osteolytic bone metastases, and poor prognosis may be interrelated. Current risk stratification models, such as the high-risk/high-volume classification, do not account for the morphological characteristics of bone metastases. Incorporating the type of skeletal involvement may improve the accuracy of future risk classifications. This underscores the need for further research on the prognostic importance of the metastatic bone types in patients with PCa.

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Current status and challenges of peer support for young people who engage in over-the-counter medicine overdose in Japan: Practice-oriented perspectives

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Abstract: Over-the-counter (OTC) medicine overdose among adolescents and young adults is an increasingly visible concern in Japan, intersecting with suicide prevention priorities and unmet psychosocial needs. In this article, we share frontline perspectives from a semi-structured group interview with five peer supporters (women in their 20s–30s) who provide street outreach, social networking service (SNS) consultation, and drop-in place-making for young people, including those who overdose on OTC medicines. Using an inductive, data-driven thematic approach to organize participants' accounts, we highlight practice-relevant insights: *i*) an ecology shaped by offline isolation, SNS normalization, and easy access to OTC products; *ii*) low-threshold, non-judgmental engagement as a first door to care grounded in peer support principles; and *iii*) fragility and safety risks as complexity escalates, underscoring the need for structured professional backup, supervision, explicit escalation criteria, and reliable referral and crisis pathways.

***Keywords*:** outreach, social networking service (SNS), help-seeking, suicide prevention, recovery-oriented practice, negative capability

1. Introduction

Suicide prevention among adolescents and young adults remains a major public health priority in Japan (*1,2*). In parallel, over-the-counter (OTC) medicine overdose has become more visible in emergency departments and community settings as a form of distress that often does not connect readily to formal services. This pattern matters because OTC overdose may function as both a gateway to repeated self-harm and a signal of unmet support needs. In practice, many young people avoid the language of "consultation" or "support", meaning that service models that primarily wait for clinic-based help-seeking can miss those at highest risk.

National data suggest that OTC misuse and overdose is not a marginal phenomenon. A national general population survey estimated that 0.75% of respondents (approximately 650,000 people) had engaged in OTC medicine misuse/abuse in the previous year (*3*). Recent clinical work in Japan also describes an emerging profile of OTC overdose among emergency patients, reinforcing the need for prevention-oriented responses beyond acute care (*4*).

OTC products implicated in misuse in Japan span multiple categories, including antitussive/expectorant medicines (cough suppressants), combination cold remedies, antipyretic analgesics, sedatives, anti-allergy medicines (antihistamines), and caffeine products (*5*). These categories matter clinically because they are widely available, can be purchased repeatedly across retailers, and can be concealed as everyday "cold medicines", even when used for mood modulation or self-harm-related purposes. At the same time, overdose carries risks including acute toxicity, dependence-related patterns, and disinhibition, potentially amplifying further self-harm and other high-risk behaviors (*4,5*).

Online environments can further shape this ecology. Exposure to and active searching for self-harm and suicide-related information on the internet are common among young adults and are associated with individual and contextual factors (*6*). In participants' accounts, social networking service (SNS) spaces served as both an information source (*e.g.*, dosing practices) and a social context that can normalize overdose-related behaviors, while also being a channel through which outreach and consultation can reach young people who would not approach clinics, schools, or public offices.

2. Frontline perspectives from peer supporters

Peer support refers to mutual, person-centered support grounded in lived experience and an egalitarian

relationship, emphasizing hope, empowerment, and connection (*7,8*). In youth settings, peer supporters may operate as a low-threshold "first door", particularly when stigma or fear of being judged prevents formal help-seeking.

We conducted a semi-structured group interview in August 2025 with five peer supporters in Japan to examine how they engage with young people who use OTC medicines for overdose, as well as the challenges encountered and support needs arising in practice. Participants were all women (mean age: 28.2 years, SD = 2.59) and had experience supporting young people who overdose on OTC medicines (mean peer-support experience: 6.8 years, SD = 3.89). The interview lasted 81 minutes and was audio-recorded, transcribed verbatim, and organized using an inductive, data-driven thematic approach (*9*). The study was approved by the Ethics Review Committee of the Faculty of Nursing and Nutrition, Shukutoku University (approval number: N25-01R1). All participants provided written informed consent. Reporting was informed by the COREQ checklist (*10*). Consistent with editorial guidance, we present these findings as practice-oriented perspectives: we extract actionable insights from participants' accounts rather than claiming transferable empirical qualitative findings.

Why focus on peer supporters' perspectives? In emerging problem areas such as OTC overdose, frontline peer workers often detect patterns earlier than formal systems because they are approached in everyday settings and online spaces. Their work is neither "clinical treatment" nor casual friendship; it is a deliberate relational practice that aims to preserve autonomy while increasing safety, and it requires its own competencies (boundary-setting, risk recognition, and linkage skills) as well as organizational support (supervision and escalation pathways). Yet these practice details and limits are often under-described in the academic literature, especially in Japan. We therefore highlight what peer supporters say they can do well, where peer work becomes fragile, and what professional backup is needed for safety and sustainability.

3. Key practice-relevant insights

Table 1 provides an overview of the full set of themes and illustrative excerpts; in the main text, we foreground four practice-relevant insights that are most actionable for research, practice, and policy.

3.1. Low-threshold engagement as a first door

Participants consistently emphasized relationship-first engagement. Many young people who overdose did not initially seek "help" in formal terms, and some actively avoided services due to fear of reprimand, labeling, or loss of autonomy. Peers therefore deliberately lowered hierarchy through everyday language, careful attention to appearance and communication style, and avoidance of evaluative words. Being with the person over time—without forcing disclosure—was described as creating psychological safety, enabling gradual self-disclosure, and easing isolation. Once a young person felt "not judged", conversations could expand from overdose episodes to underlying stressors (*e.g.*, family conflict, school refusal, economic insecurity), making it easier to introduce options such as medical consultation or welfare support without triggering withdrawal. This relational function—connection as an intervention—reflects foundational principles of peer support (*7,8*).

3.2. Fragility when complexity and risk escalate

Peer supporters also described clear limits. When trauma, severe mental illness, developmental characteristics, or complex family adversity accumulated, engagement could become unstable and risk could rise quickly. Participants noted that interactions with authority figures may reactivate traumatic dynamics, and that system barriers sometimes narrowed safe options—for example, refusals by facilities once self-harm or overdose was disclosed. They also described emotional strain when meaningful change was slow and choices were limited, leaving peers with a sense that "waiting" might be the only possible action. These accounts underscore that peer support, while powerful relationally, is not a substitute for clinical care in high-risk contexts.

3.3. Safety work: Boundaries, triage, and supervision

To work safely, participants stressed knowledge of youth mental health and available systems, alongside practical skills: non-judgmental listening, boundary awareness, and knowing when to encourage professional assessment. They highlighted the need for shared team rules for triage and crisis response, rather than relying on individual judgment. In practice terms, this includes agreed-upon thresholds for escalation (*e.g.*, signs of acute intoxication, rapidly intensifying suicidal ideation, or repeated overdose), who to contact, and how risk information is documented and shared. Organizational practices—regular check-ins, debriefing, shared case tracking, and explicit permission to step back—were described as essential to prevent burnout, particularly given exposure to self-harm narratives and abusive online communication.

3.4. Professional backup for safe and sustainable peer work

Participants valued collaboration with healthcare and public health professionals and emphasized that peer support can remain an approachable entry point only when risk assessment and timely linkage to appropriate

Table 1. Overview of themes, subthemes, and illustrative excerpts from peer supporters' accounts

Theme	Subtheme	Illustrative excerpts
Theme 1: Ecology of OTC overdose among young people	Loneliness and lack of belonging	• There is an underlying feeling of loneliness. • They have no place to belong at school or within their family and cannot consult anyone. • If they are overdosing, they do not want people in their real-life relationships to find out.
	Social media facilitation of OTC overdose	• They obtain information from overdose posts on social media, which lowers the barrier to using. • They are influenced — or even encouraged — by people they admire on social media. • Media and social media portrayals can make overdose seem "fashionable".
	Ease of access to OTC medicines	• Unlike alcohol, tobacco, or illicit drugs, OTC medicines have few age restrictions or legal barriers, making it easy to start. • Some cannot go to hospital (*e.g.*, due to lack of parental support) and therefore turn to OTC medicines. • Because they are household medicines (*e.g.*, cold remedies), use can be easily concealed from caregivers.
	Escalation and high-risk behaviors	• They cannot stop overdosing; problems remain unresolved and the behaviour escalates. • They may start with OTC medicines, then collect prescription drugs and take them all at once. • When their memory is impaired by drugs, they may self-harm or jump impulsively.
	Perceived "benefits" of misuse	• They can temporarily forget painful feelings. • For better or worse, they feel more able to act — even to do things they usually cannot.
Theme 2: Low-threshold engagement through egalitarian relationships	Alleviating isolation and fostering a sense of safety	• By continuing simply to be with them, they gradually began to talk about themselves. • Even if nothing can be done immediately, they stay connected in a thin but lasting way. • Some say, "My desire to die might have lessened a little".
	Egalitarian relationship like friends	• They adjust their appearance (make-up, nails) to match the young person. • Depending on the person, they speak casually (not formally). • They approach naturally while imagining the other person's standpoint.
	Natural engagement that avoids "support" framing	• They avoid high-threshold words such as "consultation" or "support". • They frame it as everyday conversation — "Let's talk a bit". • They do not force talk about misuse; they stay with the person as a place to belong. • A sense of growing together through support.
Theme 3: Fragile points and limits of peer support	Complexity of intertwined needs	• Family environment, mental illness, developmental disorders, and other factors are intertwined. • Some have suicidal ideation and complex feelings, such as overdosing intentionally to be hospitalised. • Listening can trigger flashbacks of past verbal or physical abuse.
	Barriers to collaboration with families and social resources	• If there is overdose or self-harm, some facilities refuse admission. • Parents are also confused and struggle with how to respond.
	Prolonged support and a sense of helplessness	• When there is nothing to do, all they can do is wait. • They regret that the young person could not stay in a safer place with more supportive connections.
Theme 4: Knowledge and skills required for safe practice	Need for professional knowledge	• Basic knowledge is needed (mental illness, developmental disorders, and available welfare systems). • Sometimes we feel that knowledge of counseling and other areas is necessary.
	Interpersonal helping skills	• Most important is to listen without denying or judging (active listening). • They try to maintain appropriate distance and boundaries.
Theme 5: Psychological burden and coping among peer supporters	Risk of burnout	• Witnessing self-harm or suicide attempts is mentally distressing. • They may be exposed to verbal abuse and harsh words.

Table 1. Overview of themes, subthemes, and illustrative excerpts from peer supporters' accounts (continued)

Theme	Subtheme	Illustrative excerpts
	Team support and self-care	• Staff check in with each other ("Are you okay?"), share information, and do not carry cases alone. • They intentionally create time away from work.
Theme 6: Professional backup and collaboration as a safety net	Improving support quality through collaboration	• It was helpful to join hospital case conferences and discuss post-discharge life together. • Professional advice from public health nurses is very helpful.
	Service users' needs for professional involvement	• Many girls seem to want to speak with a female nurse. • They may want not only peers but also professionals to listen.

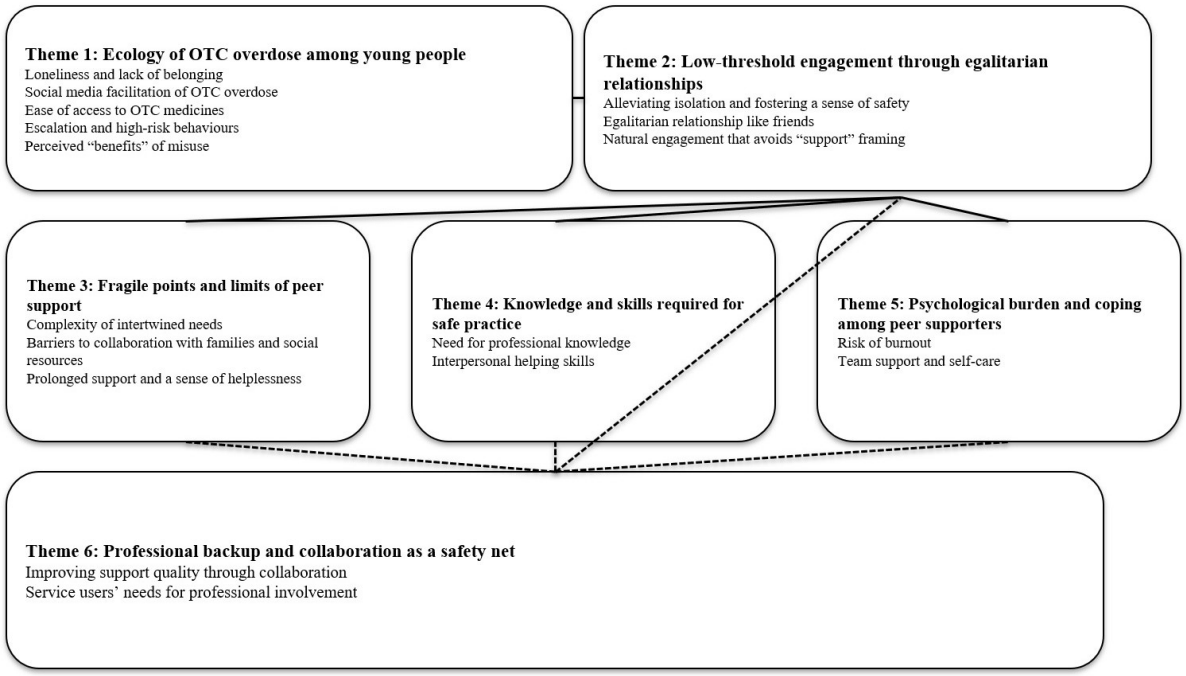

Figure 1. Inductively derived conceptual diagram of peer support for young people who overdose on over-the-counter (OTC) medicines. Solid arrows indicate the thematic pathway described by participants, from the ecology of OTC overdose (Theme 1) to low-threshold peer engagement (Theme 2) and the points where peer work becomes fragile (Themes 3–5). Dashed arrows indicate professional backup and collaboration (Theme 6) as a safety net that supports peer work across themes by enabling real-time crisis consultation, supervision, and concrete referral pathways.

services are feasible. They identified concrete needs for practice, including access to real-time crisis consultation, supervision, and reliable referral pathways that remain available even after overdose or self-harm is disclosed. We summarize the relationships among these insights in an inductively derived conceptual diagram (Figure 1), intended as a descriptive aid rather than a formal theoretical model.

4. Implications and call to action

OTC overdose among young people should not be framed as a medication issue alone. Easy access intersects with offline isolation and the pull of SNS communities that provide validation and practical know-how (*4,5*). This helps explain why models that primarily wait for clinic-based help-seeking may miss those at highest risk, and why outreach and SNS-based peer contact can function as a first door. For practitioners, the priority is to embed peer support within integrated support systems, so that relational engagement is paired with safety infrastructure.

For peer supporters, the practical challenge is to stay engaged without over-involvement and burnout. When uncertainty cannot be resolved quickly, peers may need the capacity to remain with not-knowing without rushing to premature solutions — Bion's stance of listening "without memory or desire", that is, an open stance that brackets prior assumptions and immediate solutions while staying with what emerges in the moment (*i.e.*, negative capability) (*11*) — while maintaining clear boundaries. Programs should

position peer support as a hub within an integrated network, with explicit escalation criteria, supervision, and reliable referral and crisis pathways so that peers can preserve the relational strengths of companionship while ensuring timely linkage to professional services when risk rises.

In practical terms, integrated support means that peer programs have named clinical and public health counterparts who can: (a) provide same-day consultation during crises, (b) accept referrals without excluding young people solely because overdose has occurred, and (c) co-develop shared plans for aftercare and relapse prevention. For policymakers and system leaders, actionable steps include strengthening low-threshold entry points (street outreach and SNS consultation), clarifying responsibilities and information-sharing rules across agencies, and supporting workforce sustainability through funded supervision structures. For researchers, the accounts reported here support implementation-focused studies that evaluate how professional backup, referral agreements, and escalation protocols affect outcomes such as linkage to care, repeat overdose, and peer supporters' wellbeing.

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Global health systems research symposium in Nagasaki, Japan: Building momentum for health systems strengthening and commitment to core values of global health amid headwinds

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Abstract: Since 2025, in addition to financing, the core values of global health—including community engagement, equity, evidence-informed practices, and multilateral collaboration—have been challenged by powerful global leaders. The 8th Global Symposium on Health Systems Research (HSR2024), held in Nagasaki, Japan, in November 2024, generated momentum for health systems strengthening (HSS) not only at the national and subnational levels but also globally, despite growing headwinds. HSR2024 deepened the discussions on key contemporary HSS aspects, including community engagement, health systems resilience in the face of crises, equity, and evaluation of the impacts of HSS interventions from a cross-national perspective. Notably, the Symposium pursued people-centered and rights-based approaches to civic participation in health systems planning and policymaking, and emphasized the crucial interlinkage between health security, including climate resilience and pandemic preparedness, and HSS. By addressing these issues, HSR2024 effectively revitalized the global community's commitment to the core values of global health.

***Keywords*:** health systems strengthening (HSS), global symposium, planetary health, community engagement, health systems resilience

1. Introduction

Since 2025, global health has faced severe challenges. Abrupt cuts to development assistance for health (DAH) by the United States (U.S.) and European donor countries have created a financial shortfall that has been difficult to offset. Beyond the financial impact, there are scholarly critiques that administrative orders and directives issued by U.S. leaders have raised serious concerns about core values of global public health, including community engagement, equity, evidence-informed practices, and multilateral collaboration (*1*). These include the Presidential Executive Order (EO) 14169 (*2*), EO14151 (*3*), the memorandum to reinstate the Mexico City Policy (commonly called the Global Gag Rule or GGR) (*4*), EO14168 (*5*), the Center of Disease Control and Prevention (CDC) internal directives under EO14168 (*6*), and EO14155 (*7*).

The policy intent of EO14169 (*2*) is to freeze operations of the U.S. Agency for International Development (USAID), which has led to a sharp reduction in its operational capacity, thereby affecting the global development agenda, including global health (*1,8*). EO14151 (*3*) aims to terminate the application of diversity, equity, and inclusion (DEI) policies within the U.S. federal government. While many federal agencies dismantled DEI programs in response to EO14151, multiple federal lawsuits were filed challenging its legality (*9*). The presidential memorandum (*4*) intends to reinstate the GGR and to prohibit foreign non-governmental organizations (NGOs) receiving U.S. assistance from engaging in abortion-related activities as part of the promotion of sexual and reproductive health and rights (SRHR). It has been actively implemented and expanded beyond its traditional focus on abortion-related services to encompass programs associated with gender ideology and DEI (*8*). The downstream effects of EO14151 and the memorandum on global health—particularly with regard to engagement of marginalized populations and equity in access to healthcare—have

been the subject of scholarly critique and policy debate (*1,8*). Empirical evidence from reviews of meta-analyses and large-scale studies indicates that diversity in the health workforce improves healthcare performance and outcomes (*10*). In addition, a scoping review found that development and implementation of the GGR were consistently associated with adverse effects on health system functioning and outcomes (*11*).

EO14168 (*5*) and the related directives issued by the CDC (*6*) seek to restrict the use of DEI-related terminology in scientific communications and to rescind guidance employing terms including "gender", "transgender", "pregnant person", and "LGBT". These measures have been fully implemented and have been the subject of scholarly critique and policy debate concerning their implications for the scientific integrity of public health research and data reporting (*12*). Finally, EO 14155 (*7*) mandates withdrawal of the United States from the World Health Organization (WHO), a process completed in January 2026 (*13*). The WHO possesses a unique and central normative authority in global health, even though the implementation of its legally binding instruments—such as the International Health Regulations (IHR)—depends on adoption and compliance by its Member States. Accordingly, the United States' withdrawal from the WHO has been the subject of scholarly critique and policy debate, with concerns that it may negatively affect the Organization's critical capacity as well as broader global health governance (*1,8*).

Health systems strengthening (HSS) has long been a central priority in global health and is widely regarded as a linchpin of all health programs. It has also been a key agenda in global health diplomacy, promoted by entities such as the G7 and G20 (*14*). Conceptually, HSS is positioned as a concrete means of achieving the aspirational objectives of Universal Health Coverage (UHC) and health security (*15*). Today, health systems worldwide face numerous challenges, including an increasing frequency of public health emergencies such as pandemics; climate change and environmental degradation; growing inequalities within and between countries; geopolitical tensions and conflicts; human migration and displacement; and global population aging and urbanization. The COVID-19 pandemic exposed two major weaknesses in health systems: insufficient resilience and surge capacity in the face of crises, and persistent inequalities of access to healthcare and countermeasures, such as vaccines (*16*).

HSS also faces a long-standing funding gap, as the share of DAH allocated to HSS has remained limited. Of the US$925.9 billion DAH cumulatively disbursed between 2000 and 2020, only US$128.09 billion (13.8%) was directed toward HSS, compared with US$396.51 billion (42.8%) for infectious disease control and US$248.77 billion (26.9%) for maternal and child health (Figure 1) (*17*). The global health crisis since 2025 has further exacerbated uncertainty surrounding global financing and political commitment for HSS (*1,18*), while a new initiative calling for more ownership of low- and middle-income countries (LMICs) in global health and development financing is emerging (*19*).

Against this backdrop, the 8th Global Symposium on Health Systems Research (HSR2024), held in Nagasaki, Japan, in November 2024, generated the momentum for HSS not only at the national and subnational levels but also globally, despite growing headwinds. The Symposium aimed to revitalize global commitments to health equity and health for all, evidence-informed practices (*20*), and multilateral collaboration, to realize

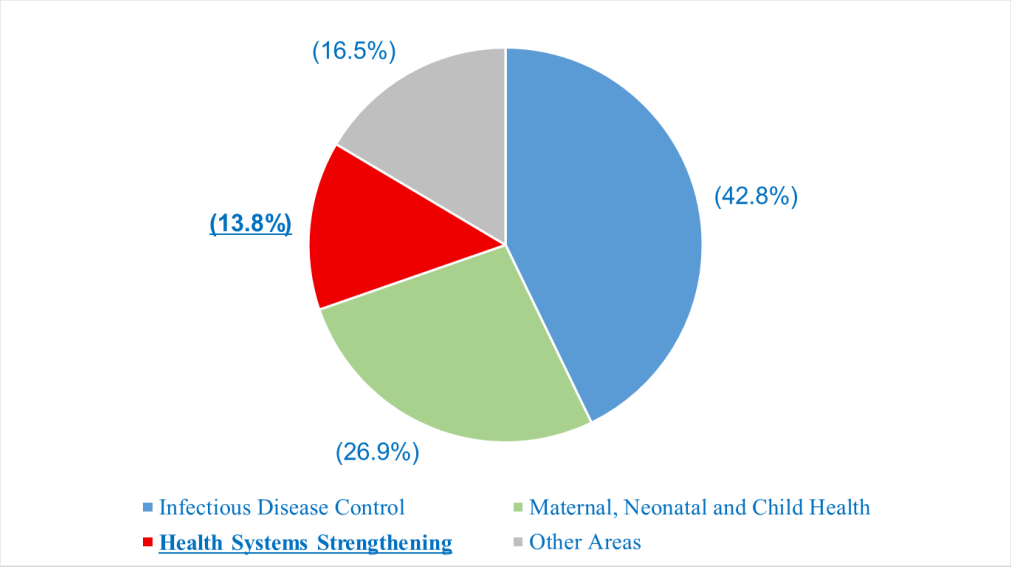

Figure 1. Development assistance for health (DAH) cumulatively disbursed to different health programmes from 2000 to 2020. *Data Data Source*: Institute for Health Metrics and Evaluation (IHME) Financing Global Health, 2025. *https://www.healthdata.org/research-analysis/library/financing-global-health-2025-cuts-aid-and-future-outlook*

sustainable health systems. In this Correspondence, we present the major findings of the Symposium in relation to contemporary debates on HSS in recent literature.

2. Outline of the 8th Global Symposium on Health Systems Research (HSR2024)

HSR2024 was organized by Health Systems Global (HSG) and co-hosted by Nagasaki University and Japan International Cooperation Agency (JICA) under the main theme, "*Building Just and Sustainable Health Systems: Centering People and Protecting the Planet*". Four sub-themes encompassed: *i*) planetary health; *ii*) justice, inclusion, and belonging; *iii*) governance, policy, and institutional frameworks; and *iv*) knowledge for just health systems (*20*). In total, 1,646 participants attended from 110 countries, with 47% from high-income countries (HICs) and 53% from LMICs. Participants from educational and research institutions accounted for 52%, followed by those from international NGOs (13%), government agencies (11%), and multilateral development agencies and private corporations (8% each).

Among the 58 organized sessions and 25 capacity-strengthening sessions—the most structured components of the Symposium's program—the most frequently addressed aspects were community engagement (13 organized and 7 capacity-strengthening sessions), health systems resilience in the face of crises (13 and 5, respectively), equity (9 and 2, respectively), and the evaluation of the impacts of HSS interventions (2 and 7, respectively). Below, we provide a concise summary of the debates that took place in HSR2024 under each common aspect, along with the corresponding recent literature. Table 1 summarizes these four common aspects and the content of the debates.

3. Community engagement

This aspect was primarily framed in the context of promoting equity and social justice in health service provision, grounded in people-centered and rights-based approaches to civic participation in health systems planning and policymaking. Three organized sessions focused on vulnerable populations, including migrants, refugees, and individuals with physical or mental disabilities. The systematic elaboration of local knowledge, encompassing civil society knowledge and indigenous knowledge, and its integration into planning and policymaking were examined in two organized sessions.

Capacity-strengthening sessions introduced a wide range of practical tools to facilitate community engagement, including co-production workshops, Science Shops (facilities that provide participatory research support in response to concerns raised by civil society), designathons (collaborative events where community participants develop innovative design solutions for specific health challenges, similar to hackathons), participatory economic evaluations, art-based participatory methods, and decolonial feminist futuring (a radical approach to envisioning and constructing futures that dismantle intersecting systems of oppression such as colonialism, patriarchy, and racism). Civil society organizations, the second largest participant category, were the primary organizers of these sessions, reflecting the broader interest of this segment in justice, inclusion, and belonging within health systems.

Existing literature addresses community participation in the context of trust-building (*21*), engagement in health system governance and accountability assurance (*22*), and community health cadres as an essential

Table 1. Main aspects of health systems strengthening (HSS) addressed and debated in the 8th Global Symposium on Health Systems Research (HSR2024)

Main aspects addressed and debated	Contents of debates
Community engagement	● People-centered and rights-based approaches to civic participation in health systems planning and policymaking. ● Systematic integration of local knowledge in planning and policymaking. ● Inclusion of vulnerable populations, *e.g*., migrants, refugees, and individuals with disabilities. ● Practical tools to facilitate community engagement.
Health systems resilience in the face of crises	● Planetary health encompassing both health system adaptation to climate change impacts and mitigation through healthcare decarbonization. ● Responsiveness to conflict and humanitarian emergencies, limited statehood, and migration. ● Integrating resilience dimensions into the Health System Performance Assessment (HSPA). ● Frameworks for assessing and strengthening health system resilience. ● Interlinkage between health security and HSS
Equity	● Integration of equity perspectives into health policy and systems research (HPSR), particularly through tools promoting fairness and equity in conducting HPSR. ● Equity in relation to health taxation (distributional equity), corruption, access to digital technologies, private sector engagement, and gender responsiveness of health systems.
Evaluation of HSS interventions	● Development of mathematical modelling to quantify the impacts of HSS interventions. ● Effective use of qualitative data in HSS evaluation.

component of community health systems (*23*). However, conceptualizations of this aspect in health system planning and policymaking, as well as practical tools to ensure it, remain scarce, highlighting the novel contribution of HSR2024 in emphasizing this aspect as an essential component of contemporary HSS.

4. Health systems resilience in the face of crisis

This aspect was primarily framed within the context of planetary health, with seven sessions focusing on the climate crisis. Notably, two sessions addressed not only health system adaptation to climate change impacts but also mitigation through healthcare decarbonization. Other crises discussed included conflict and humanitarian emergencies, limited statehood, and migration. One session examined how to integrate resilience dimensions into the Health System Performance Assessment (HSPA) framework. Several frameworks for assessing and strengthening health system resilience were presented, commonly encompassing key elements such as routine and emergency planning, availability of material and financial resources, human resource capacity, dedicated leadership, and community capabilities.

Notably, the National Center for Global Health and Medicine (NCGM) and the National Institute of Infectious Diseases (NIID) of Japan jointly organized a satellite session to launch the Japan Institute for Health Security (JIHS) internationally, which was formed through the merger of these two organizations in April 2025 (*24*). The session explored the crucial interlinkages between health security and HSS, highlighting that functional and resilient health systems are vital for effective health security measures, such as pandemic prevention, preparedness, and response (PPPR). Community engagement was emphasized as a crucial component of health systems resilience amid crises. The session also identified opportunities to leverage pandemics to strengthen health systems.

Existing literature on health systems resilience has mostly focused on the reviews of health systems performance during the COVID-19 pandemic. A comparative analysis of 28 countries highlights multi-sectoral responses, adaptation of health systems to meet evolving community needs, preserving functions and resources to maintain routine care, and reducing health and socioeconomic vulnerability as success factors of high-performing countries (*25*). A scoping review identified the importance of improved governance and financing, empowered mid-level leadership, enhanced surveillance systems, and strengthened human resources as key components of resilience (*26*). More broadly, Blanchet *et al.* proposes a framework for resilience governance, encompassing the capacity to manage resilience (use knowledge, anticipate and cope with uncertainties, manage interdependence, and build legitimate institutions that are trusted by populations) and capacity of health systems to change (absorb shocks, adapt to lower resource situations, and transform itself to respond to changing environment) (*27*).

5. Equity

This aspect was primarily discussed in the context of integrating equity perspectives into health policy and systems research (HPSR), particularly through tools such as EquiPar, which are designed to support equitable partnerships in research projects and thereby promote fairness and equity in the conduct of HPSR. Equity was also discussed in relation to health taxation (distributional equity of costs and benefits), corruption, access to digital technologies, private sector engagement, and gender responsiveness of health systems.

Existing literature on HSS and equity mainly focuses on synergies between HSS and UHC (*28*), particularly in relation to the concept of health equity, which refers to a commitment of achieving the highest attainable standard of health as a fundamental human right and to the principle of "health for all" (*29*). Notably, the latter article emphasizes that the HSS has centered on improving health service delivery, while paying insufficient attention to the political and socioeconomic dimensions that shape global health inequities (*29*). The HSR2024's focus on justice, inclusion, and belonging within health systems may be viewed as responses by HSS stakeholders to this potential limitation.

6. Evaluation of the impacts of HSS interventions

Lastly, this aspect was discussed in two distinct directions at HSR2024. First, the Alliance for Health Policy and Systems Research, together with HSG, presented development of modelling approaches and techniques to measure impacts of HSS interventions. This initiative responds to the persistent challenge that quantifying the impact of HSS investments remains elusive. Compared to major disease-specific programs, such as immunization and control of human immunodeficiency virus (HIV) infection, tuberculosis, and malaria, which are effective in presenting health benefits, value for money, and even economic benefits in monetary terms, HSS remains uncompetitive. Second, recognizing that health systems are complex and the pathways linking HSS interventions to health outcomes are nonlinear, two sessions focused on incorporating not only quantitative but also qualitative information into HSS evaluation. Practical tools such as contribution analysis and outcome harvesting were introduced as part of complexity-aware approaches to HSS evaluation.

Existing literature highlights a divided perspective among key global health stakeholders regarding evaluation of HSS impact. Some argue that their limited investment in HSS stems from a lack of evidence, viewing HSS as an unproven and potentially risky investment, driven more by philosophy than by empirical data. Others perceive

HSS as a cross-cutting principle guiding global health investment decisions and contend that the type of evidence sought by certain funders is both unattainable and unnecessary (*30*). Meanwhile, mathematical modelling, particularly system dynamics models (SDMs) and agent-based models (ABMs), has been applied to the evaluation of HSS interventions primarily in HICs (*31*). Despite methodological challenges, its extension to LMICs has also been piloted (*32*).

7. Conclusions

In conclusion, HSR2024 deepened the discussions on key contemporary HSS topics, including community engagement, health system resilience in the face of crises, equity, and the evaluation of HSS interventions from a cross-national perspective. By addressing these issues, the Symposium effectively revitalized commitment of the global community to the core values of global health, namely community engagement, equity, evidence-informed practices, and multilateral collaboration. These major outcomes, together with the subsequent Symposium in Dubai in 2026, are expected to contribute positively to reinvigorating political momentum and financing for global HSS, despite prevailing headwinds and challenges in global health. Solid evidence on HSS will also provide a foundation for greater global health ownership by LMICs.

The symposium also served as a pivotal moment for institutional innovation in Japan, providing a platform for the international launch of JIHS and the initiation of the Japan Health Policy and Systems Research (HPSR) Forum. JIHS was established to address increasingly complex global challenges related to health security. The Forum aims to foster collaboration among national and international researchers from Japan-based institutions and disseminate scientific evidence and insights from Japan's high-performing yet often underrecognized health system, credited with the world's longest life expectancy.

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AI in clinical trials: Current status, challenges, and future directions for emergency infectious disease clinical trials — Insights from the 2025 iCROWN Symposium

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Abstract: Artificial intelligence (AI) has the potential to transform how drug development and clinical trials are conducted. The 2025 Infectious Disease Clinical Research Network with National Repository (iCROWN) Symposium held in Japan on January 26, 2026 brought together experts from academia, industry, and research ethics to discuss current applications, limitations, and ethical considerations of AI in clinical trials, with a particular focus on emergency infectious disease research. Presentations highlighted a wide range of use cases for generative AI, including protocol writing; generating and reviewing clinical trial documents such as the statistical analysis plan (SAP) and the clinical study report (CSR); patient matching; data monitoring; and query creation. These applications are expected to accelerate and streamline clinical trials while maintaining quality and reducing costs. Standardization of digital data flows in clinical trials further facilitates the adoption of AI. Drawing on the FDA–EMA guiding principles for good AI practice, discussions emphasized the importance of accountability, explainability, fairness, and generalizability, while addressing risks such as overreliance, bias, and deskilling. The symposium concluded that while AI may enable more efficient clinical trial deployment during future public health crises, its challenges must be recognized and addressed.

***Keywords*:** clinical trials, artificial intelligence, infectious diseases

The rapid advancement of artificial intelligence (AI) technology is transforming every stage of clinical research, including protocol writing, subject selection, data analysis, and safety assessment (*1,2*). Within this context, the 2025 Infectious Disease Clinical Research Network with National Repository (iCROWN) Symposium held in Japan on January 26, 2026 featured presentations and lively discussions on the current status and future prospects of AI utilization in clinical trials. Participants from academia, pharmaceutical companies, and research ethics experts shared the latest insights and case studies (Figure 1). The symposium explored how AI (including machine learning and generative AI) can streamline clinical trials while also addressing its limitations and challenges.

From an academic perspective, generative AI use cases included automated generation of the statistical analysis plan (SAP) and the clinical study report (CSR) based on study protocols; matching patients to trials and vice versa. Trends toward international standardization of study protocols (*3*) and Digital Data Flow (*4*) were explained. Pharmaceutical companies also use AI to generate various trial-related documents from study protocols automatically or to review them. Efforts are underway to explore how AI can be applied to streamline data monitoring, such as automatically generating queries for data in electronic data capture (EDC) systems, and to enhance quality control in clinical trials.

Furthermore, until approximately 2021, ethical debates surrounding healthcare-related AI primarily focused on the collection and use of personal information for purposes such as diagnostic support. In recent years, however, these discussions have significantly expanded to include clinical trials and research activities. The difficulty in discussing AI ethics in healthcare stems from factors such as the diversity of people's visions of AI and the different roles of professionals and patients. Centered on the ten principles outlined in the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) joint statement on AI in drug development, "Guiding Principles of Good AI Practice in Drug Development" (*2*), presentations at this symposium highlighted key considerations for the use of AI in drug development, including the appropriateness of judgment, decision-making and responsibility, explainability, and the need to ensure generalizability and fairness. It also addressed potential issues arising from over-reliance on AI, including deskilling (erosion of professional judgment) (*5*), diminished accountability, biased training

Figure 1. Photo of the symposium venue. The symposium was held on January 26, 2026, at the JIHS Reception Room, Tokyo. Three invited speakers and five panelists discussed the use of AI in clinical trials.

data, and possible degradation of AI performance (*2*).

The World Medical Association (WMA) and the American Medical Association (AMA) refer to AI as augmented intelligence rather than artificial intelligence, and educational settings face the urgent need to reevaluate learning assessment methods. Appropriate AI use requires responsible collaboration with AI, including the ability to critically evaluate AI outputs, procedures for managing system failures, and protocols for responding to incidents arising from AI use.

A key feature of this symposium was the sharing of the latest insights on AI use in clinical trials from academic, industry, and research ethics perspectives, followed by discussions on how we could apply them to infectious disease clinical trials during emergencies. While there is no doubt that AI will advance the streamlining and acceleration of clinical trials and drug development, the panelists re-emphasized that we must recognize its limitations and challenges. To ensure appropriate use during emergencies, it is also essential to implement AI in clinical trials during peacetime and to accumulate practical experience.

iCROWN will continue to closely monitor new trends in clinical trials and drug development in the AI era. While noting both the advantages and challenges, we will explore the future direction of clinical trials for the next pandemic.

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Correspondence			
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